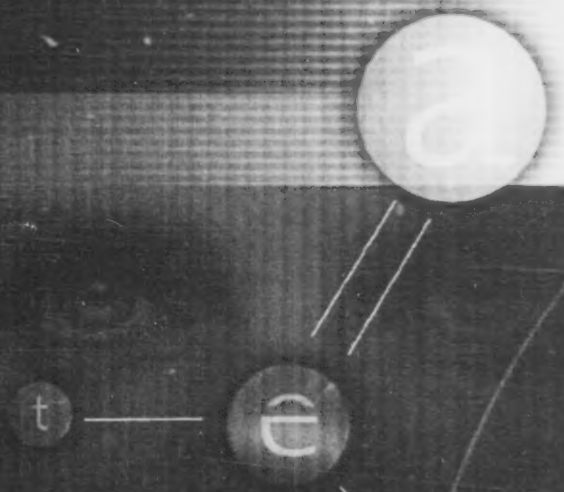
Assessment of photodynamic therapy using porfimer sodium for esophageal, bladder and lung cancers



AGENCE D'ÉVALUATION DES TECHNOLOGIES ET DES MODES D'INTERVENTION EN SANTÉ

Québec

105-06840/

Assessment of photodynamic therapy using porfimer sodium for esophageal, bladder and lung cancers

Report prepared for AETMIS
by Lonny Erickson
with Van Hung Nguyen and Séraphin Niamba

Original French version: May 2004
English translation: October 2004

Agence d'évaluation des technologies et des modes d'intervention en santé
Québec

This is the translation of an official publication produced by the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). Both the original document titled *Évaluation de la thérapie photodynamique au porfimer sodique des cancers de l'œsophage, de la vessie et du poumon* and its English version are available in PDF format on the AETMIS Web site.

Scientific Review
Véronique Déry, MD, MSc (clinical sciences), chief executive officer and scientific director
Jean-Marie R. Lance, MSc (economics), senior scientific advisor

Translation
Jocelyne Lauzière, MA, trad. a.

Page Layout and coordination
Jocelyne Guillot

Proofreading
Suzie Toutant

Communications and Dissemination
Richard Lavoie, MA (communications)

For further information about this publication or any other AETMIS activity, please contact:

Agence d'évaluation des technologies et des modes d'intervention en santé
2021, avenue Union, bureau 1040
Montréal (Québec) H3A 2S9

Telephone: (514) 873–2563
Fax: (514) 873–1369
E-mail: aetmis@aetmis.gouv.qc.ca
Web site: www.aetmis.gouv.qc.ca

How to cite this document:

Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS). *Assessment of photodynamic therapy using porfimer sodium for esophageal, bladder and lung cancers.* Report prepared by Lonny Erickson with Van Hung Nguyen and Séraphin Niamba. (AETMIS 04–01). Montréal: AETMIS, 2004, x-51 pp.

Legal Deposit
Bibliothèque nationale du Québec, 2004
National Library of Canada, 2004
ISBN 2-550-42651-7 (ISBN Original edition 2–550–42481–6)

© Gouvernement du Québec, 2004.

This report may be reproduced in whole or in part, provided that the source is cited.

MISSION

The mission of the *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS) is to contribute to improving the Québec health-care system and to participate in the implementation of the Québec government's scientific policy. To accomplish this, the Agency advises and supports the Minister of Health and Social Services as well as the decision-makers in the health care system, in matters concerning the assessment of health services and technologies. The Agency makes recommendations based on scientific reports assessing the introduction, diffusion and use of health technologies, including technical aids for disabled persons, as well as the modes of providing and organizing services. The assessments take into account many factors, such as efficacy, safety and efficiency, as well as ethical, social, organizational and economic implications.

EXECUTIVE

Dr. Luc Deschênes
Cancer Surgeon, President and Chief Executive Officer of AETMIS, Montréal, and Chairman, Conseil médical du Québec, Québec

Dr. Véronique Déry
Public Health Physician, Chief Executive Officer and Scientific Director

Jean-Marie R. Lance
Economist, Senior Scientific Advisor

Dr. Alicia Framarin
Physician, Scientific Advisor

BOARD OF DIRECTORS

Dr. Jeffrey Barkun
Associate Professor, Department of Surgery, Faculty of Medicine, McGill University, and Surgeon, Royal Victoria Hospital (MUHC), Montréal

Dr. Marie-Dominique Beaulieu
Family Physician, Holder of the Dr. Sadok Besrour Chair in Family Medicine, CHUM, and Researcher, Unité de recherche évaluative, Hôpital Notre-Dame (CHUM), Montréal

Dr. Suzanne Claveau
Specialist in microbiology and infectious diseases, Hôtel-Dieu de Québec (CHUQ), Québec

Roger Jacob
Biomedical Engineer, Coordinator, Service des immobilisations, Agence de développement de réseaux locaux de services de santé et de services sociaux de Montréal, Montréal

Denise Leclerc
Pharmacist, Board Member of the Institut universitaire de gériatrie de Montréal, Montréal

Louise Montreuil
Assistant Executive Director, Direction générale de la coordination ministérielle des relations avec le réseau, ministère de la Santé et des Services sociaux, Québec

Dr. Jean-Marie Moutquin
Obstetrician/Gynecologist, Scientific Director, Centre de recherche, CHUS, Sherbrooke

Dr. Réginald Nadeau
Cardiologist, Hôpital du Sacré-Cœur, Montréal, Board Member of the Conseil du médicament du Québec

Guy Rocher
Sociologist, Professor, Département de sociologie, and Researcher, Centre de recherche en droit public, Université de Montréal, Montréal

Lee Soderström
Economist, Professor, Department of Economics, McGill University, Montréal

FOREWORD

ASSESSMENT OF PHOTODYNAMIC THERAPY USING PHOTOFRIN FOR ESOPHAGEAL, BLADDER AND LUNG CANCERS

Cancer, in all its forms, contributes significantly to morbidity and mortality in the Québec population. It continues to be a priority target for action, not only for health policies and health-care programs but also for research. For clinicians, access to the best techniques for obstruction of cancer cells, to ensure their patients' survival while minimizing any adverse effects, is a constant challenge. These techniques can also alleviate symptoms and ensure the best quality of life possible when progression of cancer cannot be controlled.

Such is the context surrounding the assessment of photodynamic therapy using porfimer sodium. Porfimer sodium is a photosensitizing agent approved in Canada in 1993 for three oncological indications: lung, bladder and esophageal cancers. More recently, it has also been approved for the treatment of Barrett's esophagus with dysplasia, a major risk factor in esophageal cancer.

Given that the effectiveness of this new non-invasive technology has not yet been fully demonstrated, the *Ministère de la Santé et des Services sociaux* (MSSS) asked the *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS) to examine its efficacy and its potential impact on the health network. Following standard procedure, AETMIS first reviewed the scientific literature available and then made recommendations on the introduction and management of this technology.

In conclusion, photodynamic therapy remains a promising treatment whose evolution must continue to be monitored, especially with respect to the photosensitizing agents themselves. Currently, evidence-based indications are limited to the palliative treatment of advanced esophageal cancer, and it is difficult to estimate the relative importance of this technology in the therapeutic arsenal available for the other oncological applications. A more in-depth examination should be conducted on the potential use of this technology in the treatment of Barrett's esophagus. In such case, the use of this therapy would affect a greater number of patients since this disorder may appear after gastric reflux, a very widespread problem today.

In submitting this report, AETMiS hopes to contribute to ensuring the best possible use of the different oncology resources available for the benefit of all patients with cancer.

Luc Deschênes
President and Chief Executive Officer

ACKNOWLEDGMENTS

This report was prepared at the request of the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) by **Lonny Erickson**, MSc, research consultant. We would like to mention the important contributions of Jean-Marie Lance, Dr. Véronique Déry, Van Hung Nguyen and Dr. Séraphin Niamba.

We also thank the external reviewers for their many comments, which greatly contributed to the quality and the content of this report:

Dr. Judy Dorais
Gastroenterologist, Hôtel-Dieu du CHUM, Montréal

Dr. Rita Jean-François
Pneumologist, director, Interventional bronchoscopy service, CHUM, Hôpital Notre-Dame, Montréal

Dr. Jacques Jolivet
Oncologist, Shire Biochem Inc., Laval

Dr. Paul Perrotte
Uro-oncologist, Department of urology, CHUM, Hôpital Notre-Dame, Montréal

Professor François Richard
Urologist, Department of urology and kidney-pancreas transplantation, Groupe hospitalier Pitié-Salpêtrière, Paris, France

Note that Dr. Jacques Jolivet was the external reviewer designated by the Conseil québécois de lutte contre le cancer (CQLC), an agency that works in close partnership with AETMIS in all oncology-related matters. We wish to thank the CQLC and its president, Dr. Jean Latreille, for their collaboration.

SUMMARY

DESCRIPTION OF THE TECHNOLOGY

Photodynamic therapy (PDT) is used to treat several types of cancer. It consists in marking pathological tissue with a photosensitizing agent and then selectively destroying the tissue by exposing it to a light source with a specific wavelength. This monochromatic light is normally produced by a laser or a diode laser. In general, the photosensitizing agent is systemically administered to all body cells but is preferentially retained by pathological cells.

Hematoporphyrin derivatives are used as photosensitizing agents. Approved by Canada in April 1993 for three oncological indications (lung, bladder and esophageal cancers), porfimer sodium (Photofrin®) is the most widely used agent in photodynamic therapy. More recently, it has also been approved for the treatment of Barrett's esophagus with dysplasia, a major risk factor in esophageal cancer.

Porfimer sodium is activated by a light of 630 nm, but penetration is poor at this wavelength, a serious handicap when tumours are larger and deeper. This agent has a further limitation—skin photosensitivity persisting for up to six weeks after treatment. For that reason, several research projects are striving to develop agents that do not present the disadvantages and limitations of porfimer sodium. Finally, determining the appropriate dosimetry, for both the photosensitizer and the light source, is a continual challenge and remains under investigation.

OBJECTIVES OF THE ASSESSMENT

The *Ministère de la Santé et des Services sociaux* (MSSS) asked the *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS) to evaluate the efficacy of photodynamic therapy using porfimer sodium for its approved oncological indications. This report reveals the results of the assessment, attempts to adequately situate this treatment within the therapeutic arsenal available in Québec, and presents some preliminary observations on its use for the treatment of Barrett's esophagus.

METHODOLOGY

The literature search strategy we used located two reports produced by health-technology assessment agencies: the *Comité d'évaluation et de diffusion des innovations technologiques* (CEDIT), associated with the *Assistance Publique-Hôpitaux de Paris* in France (1999), and the Institute for Clinical Systems Improvement (ICSI) in the United States (1997 and 2002). To supplement this information, we searched MEDLINE for all relevant articles published between January 1997 and December 2003. Assessment of these studies was based on the scheme for grading scientific evidence proposed in the *Canadian Guide to Clinical Preventive Health Care*.

RESULTS

With respect to ***cancers of the lung and bladder and superficial esophageal cancers***, findings seem to indicate that photodynamic therapy with Photofrin® (PDT–PF) does have a therapeutic effect but that there is insufficient evidence to conclude that it has any advantage over other available treatments.

With respect to the palliative treatment for ***advanced esophageal cancer***, studies, supported by a limited level of evidence, seem to show that the efficacy of PDT (PF) would be be analogous to that of other palliative treatments (Nd:Yag laser ablation; metal stents). The cost of treatment with PDT (PF) is apparently much higher than that with stents. This important factor, combined with the fact that stents are easy to use and already in widespread use, diminishes both the interest in using PDT (PF) for this indication and the probability that it will adopted in the current context. Nevertheless, PDT (PF) could be used as a complementary therapy when other treatments are contraindicated.

The recent approval of PDT (PF) in Canada for a new indication—***Barrett's esophagus***—raises important issues. A more in-depth examination will need to be conducted of the long-term efficacy of PDT for this indication and of its place in the current therapeutic arsenal, which already offers several possible treatments. These issues should preferably be reviewed in a separate assessment report.

Finally, there seems to be a near consensus in all the literature reviewed that the field of application of PDT is likely to expand and undergo many technological developments, especially with respect to the photosensitizing agents used, which may lead to its increased use in the years to come. Photodynamic therapy is not expected to replace surgery, radiotherapy or chemotherapy; but rather, to be used as a complementary treatment. Still, we will need to obtain stronger scientific evidence of the advantages of PDT over other treatments and to examine its impact on the Québec health-care system before its use can be justified for these new applications.

RECOMMENDATIONS

In light of this analysis, AETMIS recommends the following:

- For *the treatment of lung and bladder cancers and superficial esophageal cancers*, PDT (PF) should be used only for clinical research purposes and should not be authorized for public coverage;
- For *the palliative treatment of advanced esophageal cancer*, PDT (PF) should be considered a possible option when recognized treatments are contraindicated and should undergo further clinical research;
- For *the treatment of Barrett's esophagus*, PDT (PF) should be fully assessed before it is introduced into current practice.
- A technology watch should be implemented to track technological advances in PDT in general and its new applications in particular.

CONTENTS

MISSION i
FOREWORD iii
ACKNOWLEDGMENTS iv
SUMMARY v
ABBREVIATIONS ix
GLOSSARY x
1 INTRODUCTION 1
2 OBJECTIVES OF THE ASSESSMENT 2
3 PHOTODYNAMIC THERAPY 3
3.1 General aspects 3
3.1.1 Molecular reactions: Activation of the photosensitizer 3
3.1.2 Production of phototoxic effect 4
3.1.3 Tumour-destruction mechanisms 4
3.2 Photosensitizers 4
3.2.1 Porfimer sodium (photofrin) 4
3.2.2 Other photosensitizers 5
3.3 Light sources for PDT 5
3.3.1 Lasers 5
3.3.2 Other light sources 6
3.3.3 Light delivery to target tissue 6
3.4 Dosimetry 6
4 APPROVAL STATUS FOR PORFIMER SODIUM 7
4.1 Approved therapeutic indications 7
4.2 Coverage and use in Québec and other Canadian provinces 7
5 BURDEN OF TARGETED DISEASES: EPIDEMIOLOGICAL DATA 8
5.1 Esophageal cancer 8
5.2 Lung cancer 9
5.3 Bladder cancer 9
6 METHODOLOGY 10
6.1 Research strategy 10
6.2 Scientific-evidence grading scheme for primary studies 10
7 SUMMARY OF ASSESSMENT-AGENCY REVIEWS AND OF PRIMARY STUDIES 12
7.1 Esophageal cancer 12
7.1.1 Summary of assessment-agency reviews 12
7.1.2 Recent primary studies 12
7.2 Lung cancer 15
7.2.1 Summary of assessment-agency reviews 15
7.2.2 Recent primary studies 15

7.3 Bladder cancer 17
7.3.1 Summary of assessment-agency reviews 17
7.3.2 Recent primary studies 17
8 ECONOMIC ASPECTS 19
8.1 Cost and use of the therapy 19
8.2 Cost-effectiveness 20
8.3 Budgetary impact of PDT use in Québec 20
9 DISCUSSION 21
9.1 Esophageal cancer 21
9.1.1 Advanced cancers 21
9.1.2 Superficial cancers 22
9.2 Lung cancer 22
9.3 Bladder cancer 22
9.4 Barrett's esophagus: new indication for PDT (PF) 23
9.5 General considerations 24
10 CONCLUSIONS AND RECOMMENDATIONS 25
APPENDIX A: ICSI SCHEME FOR GRADING SCIENTIFIC EVIDENCE 26
APPENDIX B: GRADING SCHEME FOR LEVELS OF EVIDENCE USED BY THE *CONSEIL QUÉBECOIS DE LUTTE CONTRE LE CANCER* (CQLC) 27
APPENDIX C: DETAILS OF SELECTED PRIMARY STUDIES ON ESOPHAGEAL CANCER 28
APPENDIX D: DETAILS OF SELECTED PRIMARY STUDIES ON LUNG CANCER 34
APPENDIX E: DETAILS OF PRIMARY STUDIES ON BLADDER CANCER 37
APPENDIX F: TNM CLASSIFICATION FOR MALIGNANT TUMORS 39
APPENDIX G: COST COMPARISON OF PHOTOFRIN-MEDIATED PDT FOR LUNG CANCER (ACCORDING TO AXCAN PHARMA) 42
REFERENCES 43

LIST OF FIGURE AND TABLES

Figure 1: Photodynamic process 3

Table 1: Most widely used photosensitizers in PDT 5
Table 2: Esophageal cancer: Incidence and mortality in Québec and Canada, 2002 8
Table 3: Lung cancer: Incidence and mortality in Québec and Canada, 2002 8
Table 4: Bladder cancer: Incidence and mortality in Québec and Canada, 2002 9
Table 5: Modified grading scheme according to level of evidence 11
Table 6: Selected studies on the effects of PDT (esophageal cancer) 13
Table 7: Selected studies on the effects of PDT (PF) (lung cancer) 16
Table 8: Selected studies on the effects of PDT (PF) (bladder cancer) 18
Table 9: Monetary value of cost items 19

ABBREVIATIONS

5-ALA:	5-aminolevulinic acid
AFSSAPS:	*Agence française de sécurité sanitaire des produits de santé* (France)
ANAES:	*Agence nationale d'accréditation et d'évaluation en santé* (France)
BCG:	Bacillus Calmette-Guérin
CEDIT:	*Comité d'évaluation et de diffusion des innovations technologiques* (France)
Cis:	Carcinoma *in situ*
DHE:	Dihematoporphyrin ether
HpD:	Hematoporphyrin derivative
ICSI:	Institute for Clinical Systems Improvement
INSPQ:	*Institut national de santé publique du Québec*
LDL:	Low-density lipoprotein
MEB:	Medicines Evaluation Board (Netherlands)
MPM:	Malignant pleural mesothelioma
NCIC:	National Cancer Institute of Canada
Nd:YAG:	Neodymium:yttrium-aluminum-garnet
PDT:	Photodynamic therapy
PDT (PF):	Photodynamic therapy using Photofrin
PF:	Photofrin
RT:	Radiotherapy
TCC:	Transitional cell carcinoma
TNM:	Tumours-Nodules-Metastases

GLOSSARY

Photosensitizing agent
A molecule capable of storing light energy and being activated by light, thus working well in numerous biochemical combinations.

Apoptosis
Genetically programmed cell death, ending the normal cycle of a cell.

Dysphagia
Difficulty swallowing.

Dysplasia
Abnormal development or uncontrolled growth of adult cells that may progress to a precancerous state.

Hematoporphyrin
Porphyrin isolated from blood.

Mesothelioma
Neoplasm (tumour) invading the endothelium of the major serous membranes (pleura, pericardium or peritoneum).

Papilloma
Tumour caused by a human papillomavirus infection.

Porphyrin
A compound formed of four pyrrolic rings linked by four methene bridges and synthesized in all tissues, especially in liver tissue and erythropoietic tissue.

Stenosis
Abnormal narrowing of an orifice, a canal or a hollow organ.

1 INTRODUCTION

Photodynamic therapy (PDT) is used to treat several types of cancers, particularly lung, bladder and esophageal cancers. This therapy consists in marking pathological tissue with a photosensitizing agent and then selectively destroying the tissue by exposing it to a light source with a specific wavelength [Courtay et al., 1999]. In general, this drug is systemically administered to all body cells but is preferentially retained by pathological cells.

Hematoporphyrin derivatives are used as photosensitizing agents. In Canada, porfimer sodium (Photofrin®) is the most widely used drug in photodynamic therapy. It is marketed by the pharmaceutical firm Axcan Pharma (Mont-Saint-Hilaire, Québec, Canada).

The *Ministère de la Santé et des Services sociaux* (MSSS) asked the *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS) to evaluate the efficacy of photodynamic therapy using porfimer sodium for its approved oncological indications in Canada. This request resulted from a partnership proposal that Axcan Pharma submitted to the MSSS to aid implementation and use of Photofrin. Axcan Pharma stated that it was willing to supply diode-laser devices to several hospitals in order to expand the use of this drug, to which it had acquired commercial rights.

2 OBJECTIVES OF THE ASSESSMENT

This report has two objectives: (1) to provide a literature review of the current state of the scientific evidence on the efficacy and effectiveness of Photofrin for the indications recognized in Canada, and (2) to estimate how much the use of this drug would cost Québec. An attempt will also be made to estimate the place of photodynamic therapy (PDT) in Québec's therapeutic arsenal and its potential impact on Québec's health-care system.

Photofrin was approved by Health Canada in March 2003 for a new indication: the treatment of Barrett's esophagus [Axcan Pharma, 2003]. Although this possible application of PDT is not the major topic of our analysis, its use will have a potentially significant impact on our health-care system. Some specific observations about this indication will therefore be included in this report.

3 PHOTODYNAMIC THERAPY

3.1 GENERAL ASPECTS

Photodynamic therapy (PDT) uses a photosensitizing agent that concentrates in pathological tissue. This agent is then activated by a light with a specific wavelength, triggering the production of reactive oxygen molecules and a cascade of events that destroy cancer cells.

Photodynamic therapy requires three components:
1) a monochromatic light;
2) a photosensitizing drug; and
3) oxygen.

3.1.1 Molecular reactions: Activation of the photosensitizer

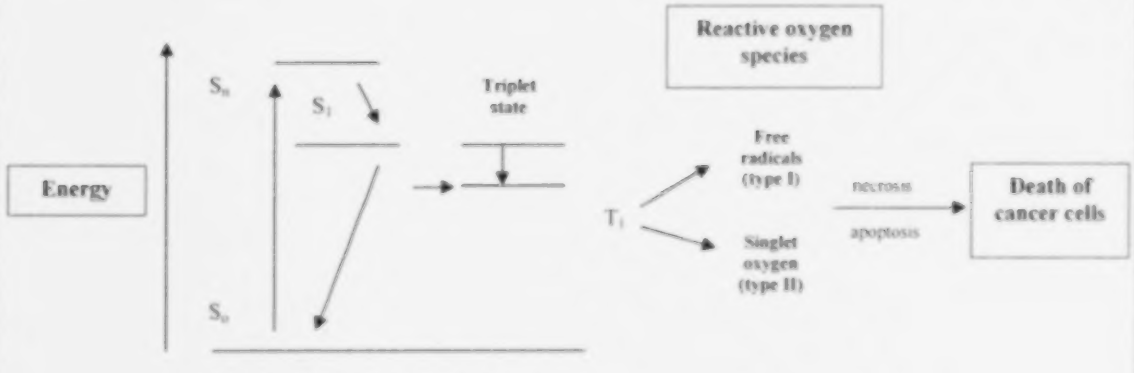
The photodynamic process is illustrated in figure 1. In the first step, a photon is absorbed by the photosensitizer, which passes from its ground energy state (S_0) to a higher energy state (S_n, S_1), called "excited singlet" state. Two events may now occur: the agent either returns to its original state by emitting energy in the form of fluorescence or heat, or it is elevated to its more stable "triplet" (T_1) state.

The triplet state leads to two possible reactions with other molecules [Sibata et al., 2001]:

1. electron transfer (type I reaction), producing free radicals that proceed to interact with the oxygen; or
2. energy transfer to an adjacent oxygen molecule (type II reaction), producing singlet oxygen ($^1O_2$).

FIGURE 1

Photodynamic process



3.1.2 Production of phototoxic effect

Singlet oxygen is a very reactive and toxic oxygen species [Foote, 1991] that destroys cancer cells, which retain the photosensitizing drug [Rivellese and Baumal, 2000; Sharman et al., 1999; Marengo et al., 1994]. Although the precise mechanism for cytotoxicity is still unknown, we do know that several cell components, such as proteins, lipids and nucleic acids, undergo reactions that trigger the lethal process of cellular oxidation [Sibata et al., 2001]. Several research studies have indicated that PDT can also induce an apoptotic response [Sibata et al., 2001; Dougherty et al., 1998], which may be associated with mitochondrial reactions [Kessel and Luo, 1998].

3.1.3 Tumour-destruction mechanisms

Besides its direct effect on cancer cells, PDT produces two other tumour-destruction mechanisms [Sibata et al., 2001; Dougherty et al., 1998; Savary et al., 1998]: (1) destruction of tumour blood vessels (leading to hypoxia) and (2) inducement of an immune response. Immediate destruction of the peritumoural vasculature is a fundamental factor in the efficacy of PDT [Lightdale et al., 1995]. Several studies underway are attempting to shed greater light on these particular modes of action.

3.2 PHOTOSENSITIZERS

The first photosensitizers used were derivatives of porcine hemoglobin [Dougherty et al., 1998; Marengo et al., 1994]. These porphyrin polymers are enriched and partially purified forms of hematoporphyrin.

3.2.1 Porfimer sodium (Photofrin)

Photofrin (porfimer sodium) was the first PDT agent to be approved in Canada. This drug is a purified mixture of hematoporphyrin (a derivative of porcine hemoglobin). Photofrin II is a more purified version of Photofrin. The abbreviation DHE (dihematoporphyrin ether) also designates Photofrin.

Research studies in molecular biology have shown that porphyrins can be recognized by receptors expressed on the surface of cancer cells. This recognition is not possible on healthy cells [Dougherty et al., 1998; Diamond et al., 1972; Lipson and Baldes, 1960]. The affinity of hematoporphyrin for cancer cells explains the therapeutic effect of photosensitizers exposed to a light source.

In the vascular system, porphyrins bind to the receptors of low-density lipoproteins (LDL) through covalent bonds [Diamond et al., 1972]. The substantial increase in the number of LDL receptors in malignant cells compared with those in normal cells is undoubtedly a key factor allowing photosensitizers to concentrate in tumour tissue [Savary et al., 1998; Walther et al., 1997; Marengo et al., 1994].

Photofrin is administered intravenously. Forty-eight hours must elapse before the light source can be activated (requiring two hospital stays). Clinically, Photofrin is generally activated by a 630-nm light source. At this wavelength, however, light can penetrate only from 5 to 10 mm deep, a serious shortcoming when tumours are larger or deeper [Patterson and Wilson, 1999].

Photofrin-mediated PDT has another limitation: skin photosensitivity persisting for up to six weeks after treatment. Several research groups are currently attempting to develop agents that will have neither the disadvantages nor the limitations of Photofrin. Table I presents the most widely used photosensitizers in PDT, along with their specific indications. Notice that each product has it own activation wavelength.

TABLE 1

Most widely used photosensitizers in PDT

PHOTOSENSITIZER	TRADE NAME	ROUTE OF ADMINISTRATION	WAVELENGTH (λ) FOR PDT (nm)	KNOWN THERAPEUTIC APPLICATIONS	APPROVED IN CANADA
Porfimer sodium Polyhematoporphyrin	Photofrin® Photosan®	Intravenous (IV)	630	Bladder, esophageal and lung cancers, and Barrett's esophagus	Yes
5-aminolevulinic acid (5-ALA)	Levulan®	Topical 20%, oral, IV	635	Actinic keratosis, bladder cancer	No
Tetrasodium-tetraphenyl-porphyrin sulfonate (**$TPPS_4$**)	–	Topical 2%, intralesional	630	–	No
Meta-tetrahydroxyphenyl chlorin (**m-THPC**) (**temoporfin**)	Foscan®	IV	652	Head and neck tumours, Barrett's esophagus	No
Tin ethyl etiopurpurin (**$SnET_2$**)	Purlytin®	IV	660–665	Cutaneous Kaposi's sarcoma, prostate cancer	No
N-aspartyl-chlorin e6 (**Npe_6**)	–	IV	660–665	–	No
Chloro-aluminum sulfonated phthalocyanine (**CASPc**)	–	IV	670–675	–	No
Benzoporphyrin derivative monacid (**BPD-MA**), verteporfin	Visudyne®	IV	690–692	Macular degeneration	Yes
Texaphyrin lutetium, motexafin lutetium	Lutrin®	IV	720–760	Melanomas, breast cancer	No

Sources: Ceburkov and Gollnick, 2000; Sibata et al., 2002; Health Canada, Therapeutic Products Directorate

3.2.2 Other photosensitizers

Photosensitizers other than Photofrin are generally activated at higher wavelengths; they are characterized by faster clearance from the body, and they have better pharmacokinetic properties in that they cause fewer skin-photosensitivity reactions than Photofrin [Sibata et al., 2001]. Randomized clinical trials are expected to be conducted over the next decade to examine the efficacy of these new photosensitizers, and several of them will likely be approved in Canada for different forms of cancer. For the time being, however, it is still difficult to estimate the costs of these drugs and the equipment (e.g., lasers) they will require.

3.3 LIGHT SOURCES FOR PDT

Several light sources can be used to activate PDT photosensitizers. Each drug requires a specific wavelength and intensity. The wavelength emitted by the activation light source determines whether the light can penetrate the skin deeply enough to reach the cancer cell [ANAES, 1997].

3.3.1 Lasers

Several types of lasers are used in medicine. They are differentiated by their active mediums: there are solid lasers, gas lasers, liquid lasers and semiconductor diode lasers.

3.3.1.1 Nd:YAG

The name Nd:YAG comes from the fact that this laser uses a crystal cylinder containing neodymium-yttrium-aluminum garnet (YAG) and that a certain amount of aluminum is replaced by neodymium (Nd). These lasers have many applications [Teppo, 1998], especially in oncology for photodynamic therapy and direct tumour ablation [CORD, 2001].

3.3.1.2 Pumped-dye lasers

These lasers use a gas medium, such as argon, mixed with a dye. The key advantage of this type of laser is that the wavelength can be adjusted by means of a tuning element or by modifying the dye [CORD, 2001]. Such a device could potentially be used for all current and future therapies.

Lasers such as Nd:YAG and tunable-dye lasers are often used in PDT, but they have certain disadvantages: they are expensive to buy and to operate [Sibata et al., 2001]. Diode lasers such as Diomed 630 nm (Diomed Inc., Cambridge, Great Britain), which are less expensive than pumped-dye lasers, are currently generating a great deal of interest.

3.3.2 Other light sources

Light sources other than lasers can be used in PDT, including LEDs (light-emitting diodes) [Patterson and Wilson, 1999]. Multiple-frequency light sources, such as slide-projector lamps with red filters, have also been investigated [Dougherty et al., 1998; McCaughan, 1972].

3.3.3 Light delivery to target tissue

There are three types of light-delivery devices: optical fibres, articulated arms and hollow waveguides. Several types of cylindrical diffusers or balloons are also used to deliver light endoscopically in the treatment of lung, esophageal and bladder cancers.

3.4 DOSIMETRY

Absorption of both the photosensitizer and the light is heterogeneous, variable and complex. Because it is virtually impossible to determine the exact levels of these two components in target tissue, it is difficult to interpret clinical-trial results [Smith and Hahn, 2002]. Several research groups are making significant headway in establishing the right dosimetry for PDT [Chen and Hetzel, 1998; Litle et al., 1998; Star, 1997].

4 APPROVAL STATUS FOR PORFIMER SODIUM

4.1 APPROVED THERAPEUTIC INDICATIONS

In Canada, porfimer sodium (Photofrin) was approved in April 1993 for oncological indications (esophageal, lung and bladder cancers) by the Canadian Health Protection Branch of Health Canada, (official Photofrin product monograph, September 29, 2000). More recently, it has also been approved for the treatment of Barrett's esophagus. This new indication will be discussed in the analysis and conclusion sections of this report.

Porfimer sodium (Photofrin) is indicated:

1) for the partial or complete reduction of obstruction in the esophagus in patients with esophageal cancer;

2) for the reduction of obstruction and symptomatic relief in patients with completely or partially obstructing endobronchial cancer and in patients who are not candidates for surgery or radiotherapy; and

3) as a second-line treatment after endoscopic transurethral surgery in patients with superficial and recurrent papillary bladder cancer who have failed to respond to standard intravesical treatment [Axcan Pharma, 2000a].

In France, Photofrin was approved in 1997 by the *Agence française de sécurité sanitaire des produits de santé* (AFSSAPS) to treat recurrent bronchial and esophageal cancers [AFSSAPS, 1997].

Both the United States and the Netherlands have approved Photofrin for palliation of esophageal cancer and for the treatment of early-stage lung cancer when patients are unable to withstand surgery and radiotherapy [MEB, 2001; FDA, 2000].

In Japan, Photofrin has been approved for stomach cancer [FDA, 2000], in addition to the indications recognized in the United States. It has also been approved in the United States, Japan and certain countries in the European Union (France, Great Britain, Netherlands, Germany) for Barrett's esophagus (stages I, II and III) [MEB, 2001; AFSSAPS, 1997].

4.2 COVERAGE AND USE IN QUÉBEC AND OTHER CANADIAN PROVINCES

Québec and Manitoba are the only two Canadian provinces whose public-health programs cover direct and indirect costs tied to Photofrin-mediated PDT[1].

This product has been on the list of prescribed medication in Québec's health-care institutions since July 1996. The *Centre hospitalier universitaire de Montréal* (Hôtel-Dieu pavilion) is the only institution that has reported using photofrin to date (i.e. only 10 patients [personal communication, Hôtel-Dieu pharmacy].

1 This situation is evolving. According to additional information obtained in June 2004, there is some very limited use of sodium porfimer in other provinces like British Columbia and Ontario, the public funding being done on a case-by-case basis.

5 BURDEN OF TARGETED DISEASES: EPIDEMIOLOGICAL DATA

5.1 ESOPHAGEAL CANCER

Squamous-cell carcinoma and adenocarcinoma of the esophagus are more prevalent in men than in women [Faivre et al., 1998] and rarely appear before the age of 25. Statistics on the incidence and mortality of esophageal cancer in Québec and Canada are presented in table 2. The survival rate is very low for this type of cancer. In 2002, the five-year case-fatality rate for esophageal cancer was 100% for untreated women and men in Canada. With treatment, the one-year rate was 83% [Peterson and Mayrand, 2000]. In Québec, this rate was 89% for men and 81% for women [INSPQ, 2001]. According to U.S. statistics for 1992–1998, the five-year survival rate for treated esophageal cancer was 13.4% for men and 13.1% for women [NCIC, 2002].

In North America, less than 10% of esophageal cancers are detected at an early stage [Sharpe and Moghissi, 1996; Moghissi, 1992]. As a result, treatment is palliative and consists in alleviating dysphagia (using a variety of means such as radiotherapy, chemotherapy, placement of stents [tubes] in the esophagus, Nd:YAG laser ablation and PDT).

TABLE 2

Esophageal cancer: Incidence and mortality in Québec and Canada, 2002

INCIDENCE				MORTALITY			
Canada		**Québec**		**Canada**		**Québec**	
Men	Women	Men	Women	Men	Women	Men	Women
980	400	204	77	1 100	400	207	65

Source: INSPQ, 2001

TABLE 3

Lung cancer: Incidence and mortality in Québec and Canada, 2002

INCIDENCE				MORTALITY			
Canada		**Québec**		**Canada**		**Québec**	
Men	Women	Men	Women	Men	Women	Men	Women
12 000	8 800	3 900	2 100	10 700	7 700	3 600	2 200

Source: NCIC, 2002

5.2 LUNG CANCER

The incidence of lung cancer varies radically from one province to another. It is expected to increase in the years to come [Statistics Canada, 2002; NCIC, 2002]. Statistics on the incidence and mortality of lung cancer in Québec and Canada are shown in table 3.

The survival rate is very low. In Canada, in 2002, the five-year fatality rate was an estimated 83% for women and 86% for men [NCIC, 2002]. In Québec, they were 85% for women and 92% for men [MSSS, 2002].

5.3 BLADDER CANCER

Statistics on the incidence and mortality of bladder cancer in Québec and Canada are shown in table 4. In 1996, 1 121 new cases for men and 356 new cases for women were reported in the *Fichier des tumeurs du Québec* (Québec's cancer registry). In 1998, these figures rose to 1 186 and 433, respectively [MSSS, 2002].

The five-year fatality rate for bladder cancer in Canada was 30% for men and 33% for women [NCIC, 2002.]. In Québec, it was 16% for men and 22% for women [NCIC, 2002].

TABLE 4

Bladder cancer: Incidence and mortality in Québec and Canada, 2002

INCIDENCE				MORTALITY			
Canada		**Québec**		**Canada**		**Québec**	
Men	Women	Men	Women	Men	Women	Men	Women
3 700	1 300	1 350	460	1 050	470	260	120

Source: NCIC, 2002

6 METHODOLOGY

6.1 RESEARCH STRATEGY

Two health-technology assessment agencies evaluated PDT (PF): the *Comité d'évaluation et de diffusion des innovations technologiques* (CEDIT), affiliated with *Assistance Publique-Hôpitaux de Paris* in France [Courtay et al., 1999], and the Institute for Clinical Systems Improvement (ICSI) in the United States [ICSI, 2002; ICSI, 1997].

The French agency reviewed primary studies published between 1986 and 1997 on esophageal cancer, Barrett's esophagus and other gastroenterological cancers (stomach, colon, rectum and upper aerodigestive tract). CEDIT analyzed these studies on the efficacy of PDT (PF) primarily on the basis of a descriptive evaluation of these studies without rating the evidence. This agency analyzed eight primary studies on esophageal cancer and seven on Barrett's esophagus.

ICSI, for its part, published an initial report reviewing primary studies published between 1981 and 1997, and then extended this period to 2002 in its updated version. The ICSI evaluation dealt with head and neck cancers, tracheobronchial and esophageal cancers, and Barrett's esophagus. The agency's literature review was based on a scale with three grades of evidence: A (randomized controlled trials), B (non-randomized controlled trials with a strong design), C (uncontrolled case-series studies or expert opinions) (*see* appendix A). This grading scheme was modified in the 2002 update, but that does not affect our analysis. The ICSI reports provide summaries of the studies undertaken for each PDT indication in question and a very brief conclusion. The procedure ICSI followed to reach those conclusions is not presented.

Given that the data in these reports were no longer current, we also searched MEDLINE for review articles or primary articles published between 1997 and December 2003 on photodynamic therapy for esophageal, bladder and lung cancers, or on oncology.

The keywords we used included *photodynamic therapy, Photofrin, dihematoporphyrin ether, porfimer sodium, oesophageal cancer, bladder cancer, lung cancer, oesophageal reflux, gastroesophageal reflux disease, neoplasm, adenocarcinoma, carcinoma, Barrett's oesophagus*. We also combined each keyword with the terms *cost-utility, cost-benefit, cost-effectiveness, cost-minimization, porfimer sodium (Photofrin I), porfimer sodium (Photofrin II), Photofrin, Photofrin®, Photofrin I, Photofrin II, PDT (Photofrin), PDT (haematoporphyrin/hematoporphyrin), PDT (dihaemato-porphyrin ether/dihematoporphyrin ether: DHE/DhE), Protoporphyrin IX (PpIX), haematoporphyrin derivative (HpD/HPD)*. We did not limit the search to any particular language. We also performed a manual search of conference proceedings and examined the bibliographies of articles and other papers we obtained to analyze the research question.

6.2 SCIENTIFIC-EVIDENCE GRADING SCHEME FOR PRIMARY STUDIES

There are several types of grading schemes (*see* Appendices A and B). We chose the one provided in the *Canadian Guide to Clinical Preventive Health* [Canadian Task Force on the Periodic Health Examination, 1994]. Although designed for studies on screening or preventive clinical practices, this scheme also allows for the classification of studies individually. Table 5 presents the modified grading scheme we used to classify primary studies according to their level of evidence.

TABLE 5

Modified grading scheme according to level of evidence

QUALITY OF STUDY RESULTS	LEVEL OF EVIDENCE
Evidence from at least one properly randomized controlled trial	I
Evidence from well-designed clinical trials without randomization	II-1
Evidence from well-designed cohort or case-controlled analytic studies	II-2
Evidence from comparisons from multiple time series or from more than one centre, whether or not an intervention was used	II-3
Opinions of respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees.	III

Adapted from the *Canadian Guide to Clinical Preventive Health*. Health Canada [Canadian Task Force on the Periodic Health Examination, 1994]

7 SUMMARY OF ASSESSMENT-AGENCY REVIEWS AND OF PRIMARY STUDIES

We examined the therapeutic efficacy of PDT (PF) by summarizing the review articles published by the two health-assessment agencies (CEDIT and ICSI) and by synthesizing the findings of selected recent primary studies (detailed in Appendices C, D and E).

7.1 ESOPHAGEAL CANCER

7.1.1 Summary of assessment-agency reviews

7.1.1.1 FRANCE: CEDIT (1997)

With respect to esophageal cancer, CEDIT mentions four fields of application of (potential) interest for PDT (PF):

1) palliative treatment of inoperable tumours to provide patients with greater well-being at the end of their lives;
2) alternative treatment when surgery is contraindicated;
3) complementary treatment to other treatments;
4) treatment for early-stage cancer lesions: carcinoma *in situ* (Tis) or submucosal tumours (T1) (*see* table F-1 in appendix F).

Palliation (advanced cancers)

The CEDIT report mentions that a randomized controlled trial comparing PDT with Nd:YAG laser oblation obtained "results in favour of PDT." In that study, PDT required fewer interventions (1.5 vs 2.4 for Nd:YAG) and caused fewer esophageal perforations [Lightdale et al., 1995]. Despite these interesting findings, CEDIT recommends using Nd:YAG as a first-line treatment for relief of dysphagia.

7.1.1.2 UNITED STATES: ICSI (1997, 2002)

Advanced tumours

The authors of the ICSI report conclude that PDT is effective for treating dysphagia in cases of advanced cancer. PDT (PF) is as effective as Nd:YAG laser ablation, and may offer the benefits of improved clinical parameters and lower complication rates. This conclusion is based primarily on two randomized trials comparing PDT with Nd:YAG laser ablation [Lightdale et al., 1995; Heier et al., 1995].

Superficial tumours

The authors of both reports conclude that early-stage esophageal tumours and adenocarcinoma associated with Barrett's esophagus respond to PDT (level of evidence equivalent to categories C/II-3) (*see* appendix A and table 5). For early-stage cancers, complete-response rates observed in the studies in question vary between 40% and 81%, with a local recurrent rate of around 30%.

7.1.2 Recent primary studies

Table 6 presents the five selected studies in which Photofrin was used. We also chose three additional studies that used agents that closely resemble Photofrin, i.e., hematoporphyrin derivative (HpD), a precursor of Photofrin, and Photosan® (a mixture of porphyrin derivatives very similar to Photofrin) [Maier et al., 2001a and b; Maier et al., 2000; Corti et al., 2000].

Two publications do not appear in this table: the first includes a single patient with esophageal cancer [Mlkvy et al., 1998], and the second includes only four cases [Scheider et al., 1997]. The second study is nevertheless relevant in terms of palliative treatment for patients who experience complications with stents. These two primary studies are detailed in tables C-2 and C-3 in appendix C. Of the seven studies reviewed, five examined the role of PDT in the palliative treatment of advanced esophageal cancers and two examined the treatment of superficial or early-stage cancers.

TABLE 6

Selected studies on the effects of PDT (esophageal cancer)

LEVEL OF EVIDENCE (study design)	AUTHORS AND NUMBER OF CASES	PDT APPLICATION STUDIED	AUTHORS' CONCLUSIONS
I (randomized) (abstract only)	Canto et al., 2002 56 cases	Use of PDT compared with stenting for palliation of dysphagia in cases of advanced cancer	Similar results for PDT (PF) and stents in terms of dysphagia relief but greater number of reinterventions with PDT. Stents are more cost-effective.
II-3 (case series)	Litle et al., 2003* 215 cases	Palliation of dysphagia in cases of advanced and inoperable cancers	PDT (PF) is a safe and effective treatment for bleeding or obstructing esophageal cancers, or both. Reinterventions may be necessary to maintain palliation of malignant dysphagia in patients who live longer than two months, and a multimodality treatment approach, which includes PDT, is common.
	Luketich et al., 2000* 77 cases	Palliation of dysphagia in cases of advanced and inoperable cancers	PDT (PF) is a safe and effective treatment for bleeding or obstructing esophageal cancers, or both. Further trials must be conducted to analyze the cost-effectiveness of this treatment and its relative contribution to patients' quality of life compared with other palliation options.
	Moghissi et al., 2000 65 cases	Palliation of dysphagia in cases of advanced and inoperable cancers	PDT (PF) is a safe and effective treatment for inoperable dysphagia. There was a regression in the stages of dysphagia and a potential prolongation of survival in patients with less advanced tumour stages.
	Grosjean et al., 1998 15 cases	Treatment of superficial esophageal and bronchial carcinomas Comparison of laser light at 514 nm and at 630 nm	PDT (PF) is effective and presents similar results with light at 514 nm and at 630 nm. Light at 514 nm could reduce the perforation rate (associated complication) in the treatment of esophageal carcinomas.
II-3 Studies on hematoporphyrin derivatives similar to Photofrin (case series)	Maier et al., 2001a; 2001b 49 cases	Comparison between HpD/Photosan and 5-ALA in advanced esophageal carcinomas (two publications with the same outcomes)	Despite the limitations of a non-randomized trial, HpD/Photosan seems to be more effective than 5-ALA for the treatment of advanced esophageal carcinomas.
	Maier et al., 2000† 119 cases	Advanced carcinomas PDT combined with radiotherapy compared with radiotherapy alone	PDT followed by radiotherapy is effective in palliating advanced esophageal cancers. Care must be taken with patient selection to prevent major complications.
	Corti et al., 2000‡ 62 cases	Use of PDT for inoperable early-stage cancers (followed by radiotherapy, if necessary)	PDT is effective for early-stage esophageal cancer. The addition of radiotherapy, when necessary, increases the complete-response rate.

* Articles by Litle, et al. [2003] and Luketich et al. [2000] may contain the same cases between 1996 and 1998.
† A hematoporphyrin derivative, Photosan® (polyhematoporphyrin), was used in this study.
‡ A hematoporphyrin derivative (HpD) was used in this study (not Photofrin).
Study details appear in appendix C.

7.1.2.1 ADVANCED CANCERS

Treatment with PDT for advanced esophageal cancers is basically palliative, and survival statistics do not generally indicate any improvement in this parameter [Luketich et al., 2000]. Three case-series studies seem to indicate that PDT (PF) would be effective for relieving dysphagia in patients presenting with inoperable or late-stage esophageal cancers.

Clinically, this translates into improved mean dysphagia scores or dysphagia-free intervals, or both. The authors conclude that PDT (PF) is a safe and effective palliative treatment for advanced, obstructing, bleeding and/or inoperable esophageal cancers [Litle et al., 2003; Luketich et al., 2000; Moghissi et al., 2000]. Moreover, the most recent publication explicitly states that PDT treatments can be repeated or combined with other available treatments (depending on the case). It also presents a treatment algorithm for choosing PDT or other available treatments [Litle et al., 2003].

7.1.2.2 Comparison with stents

A randomized trial with 56 patients (available only as an abstract), compared PDT (PF) with metal stents for palliation of dysphagia in advanced esophageal cancers. A significant reduction in dysphagia was observed in both groups. There was no survival difference. Seventeen percent of the patients treated with PDT (PF) did not respond to treatment and later received stents. Stents cost only one-third of the price of PDT and were also better in terms of cost-effectiveness. The authors conclude that PDT and stents offer similar advantages for treating dysphagia, but stents provide more marked and faster relief. In addition, PDT requires more reinterventions [Canto et al., 2002].

7.1.2.3 Palliative treatment for patients who had complications with stents

Photodynamic therapy may have another interesting palliative application in cases of advanced esophageal cancer: the treatment of patients who had complications with stents. A few cases of dysphagia caused by tumour ingrowth (i.e., tumour growing around the stent) were successfully treated [Litle et al., 2003; Luketich et al., 2000; Moghissi et al., 2000; Scheider et al., 1997]. This is a particularly interesting benefit of PDT, given the limitations of the other treatments and the possibility that Nd:YAG laser ablation may damage the stent [Luketich et al., 2000; Moghissi et al., 2000].

7.1.2.4 Superficial cancers

Two studies revealed that PDT was effective for treating superficial or inoperable early-stage tumours (response rates ranging from 37% to 68%; survival from 6 to 90 months). In both studies, response rates dropped sharply for more invasive tumours (affecting the submucosa or muscle tissue). Note that these studies compared only photosensitizers (Photofrin vs HpD) and light activated at different wavelengths [Grosjean et al., 1998; Corti et al., 2000].

7.1.2.5 Complementary aspects of PDT use

Light source and wavelength

One study compared the use of green light (514 nm) with that of red light (630 nm) to activate the Photofrin [Grosjean et al., 1998]. Green light at 514 nm penetrates esophageal tissue less deeply, which may prevent complications such as esophageal perforation. Complete-response rates were similar in both treatments. Although no major complication was identified in the study, certain histologic comparisons revealed a reduction in tissue lesions with treatment using 514-nm green light.

Number of treatment sessions

Multiple PDT treatment sessions can be administered in many situations, especially in cases of non-response to treatment or large tumours [Grosjean et al., 1998; Corti et al., 2000; Luketich et al., 2000; Moghissi et al., 2000]. For large tumours, two light-activation sessions are recommended, one directed toward the centre of the esophagus and the other directly into the tumour [Moghissi et al., 2000]. Relief of dysphasia is generally expected to last from three to four months. Afterwards, PDT can be repeated as necessary [Moghissi et al., 2000].

Combination therapies

Patients with incomplete response to PDT could benefit from a subsequent radiotherapy session. Radiotherapy can also be administered to

patients with local-tumour recurrence a few months after initial treatment [Corti et al., 2000]. With the use of Photosan (polyhematoporphyrin), a drug very similar to Photofrin, PDT followed by radiotherapy, seems to yield better results than radiotherapy alone [Maier et al., 2000].

Treatment with PDT could also be followed by placement of a stent or surgery in cases of non-response; however, PDT causes the esophagus to be less resistant, which increases the risk of perforation and major complications arising from stent placement [Maier et al., 1999].

7.2 LUNG CANCER

7.2.1 Summary of assessment-agency reviews

7.2.1.1 CEDIT

This French agency did not analyze the role of PDT (PF) in lung cancer, but it did offer some general comments. According to CEDIT, the use of PDT (PF) and other treatments (Nd:YAG laser ablation, cryotherapy and brachytherapy) are not recommended for stages I, II and III. It may be used in stage IV. Photofrin-mediated PDT is not considered a first-line treatment.

7.2.1.2 ICSI

In both reports, this U.S. agency analyzed the therapeutic effects of PDT (PF) on tracheobronchial cancer. All the selected case-series studies on this indication had a level of evidence rated as "C" (equivalent to II-3). Note that at the time of publication of this report, there were no primary randomized controlled trials on tracheobronchial cancer and statistics on the subject vary widely.

Palliation of advanced cancers

The selected studies indicate varying complete-response rates to PDT and other effects, such as decreased obstruction and improvement in quality of life, as well as outcomes similar to those produced by Nd:YAG laser ablation. In conclusion, ICSI recognizes that PDT (PF) is effective for improving patients' quality of life and reducing the size of tumours and their associated obstructions. This conclusion nevertheless raises some doubt because it is based on studies with weak evidence.

Superficial cancers

The selected studies reveal that PDT is relatively effective for producing a complete response (local destruction). They also emphasize the advantage of using PDT with other methods, such as radiotherapy and surgery, to obtain optimum long-term results. In conclusion, ICSI considers PDT (PF) to be effective for treating tracheobronchial cancers and superficial lesions. The studies examined, however, do not provide enough evidence to support this conclusion, especially given the lack of valid controlled trials.

7.2.2 Recent primary studies

Six primary studies were selected. Table 7 summarizes them according to level of evidence or study design, PDT application and authors' general conclusions.

7.2.2.1 INOPERABLE ADVANCED CANCERS

A randomized trial noted that PDT (PF) was comparable to Nd:YAG laser ablation for the palliative treatment of patients presenting with inoperable tracheobronchial obstructions [Diaz-Jiménez et al., 1999]. Observed differences were not significant.

A series of 100 patients with inoperable advanced lung cancer also obtained good response rates in terms of symptomatic relief and improved general well-being. In addition, survival was prolonged in the group that had better overall health at the beginning of the study. The authors stressed that surgery is effective for treating early-stage cancers and conclude that PDT should be used mainly for inoperable and advanced cancers [Moghissi et al., 1999].

7.2.2.2 MALIGNANT PLEURAL MESOTHELIOMA (MPM)

A non-randomized trial reported good survival rates for patients with stage I or II malignant

pleural mesothelioma treated with surgery and PDT. Survival rates were lower for patients in stage III or IV. Bronchopleural fistulas were the major complication arising from the use of PDT combined with pneumonectomy [Moskal et al., 1998].

A randomized trial examined PDT combined with surgery and immunotherapy in comparison with treatment consisting of surgery and immunotherapy alone. This study did not note improved survival or local-tumour destruction in patients with MPM [Pass et al., 1997].

7.2.2.3 Pulmonary metastases

The use of PDT (PF) to treat endobronchial metastases has been shown to be beneficial in reducing obstructions and improving quality of life [McCaughan, 1999]. These results mean that PDT could presumably be used for patients presenting with early-stage non-pulmonary cancer, but the lack of comparisons with other therapies does not allow us to draw a definitive conclusion.

7.2.2.4 Respiratory papillomas

According to a U.S. study conducted with a (non-randomized) control group, PDT (PF) would be more effective than standard treatments for destroying upper respiratory-tract tumours caused by human papillomavirus, but it would be even more effective at a higher dose (4.25 vs 3.25 mg/kg). The authors of this study are pursuing their investigations with a new photosensitizer called *meso-tetrahydroxyphenyl chlorin* (mTHPC) [Shikowitz et al., 1998].

TABLE 7

Selected studies on the effects of PDT (PF) (lung cancer)

LEVEL OF EVIDENCE (study design)	AUTHORS AND NUMBER OF CASES	PDT APPLICATIONS STUDIED	CONCLUSIONS
I (randomized)	Diaz-Jiménez et al., 1999 31 cases	Comparison with Nd:YAG laser ablation for palliation of inoperable tracheobronchial obstructions	Both treatments had similar efficacy and safety results.
	Pass et al., 1997 63 cases	Combination of PDT with surgery and immunotherapy for patients with malignant pleural mesothelioma (MPM)	Addition of PDT to surgery and immunotherapy provides no benefits in terms of survival or local destruction.
II-2 (non-randomized, controlled)	Shikowitz et al., 1998* 81 cases	Destruction of tumours in respiratory tract caused by human papillomavirus	PDT reduces the growth rate of pleural papilloma, and a higher dose increases the reduction.
II-3 (case series)	Moskal et al., 1998 40 cases	MPM treated with surgery and PDT	Good survival rate for stages I and II MPM, but poor for stages III and IV; major complications.
	Moghissi et al., 1999 100 cases	Inoperable advanced tumours	PDT gives good results for symptomatic relief of inoperable advanced tumours.
	McCaughan, 1999 40 cases	Treatment of non-pulmonary endobrochial metastases	Reduction of endobronchial obstructions with PDT and modest improvement in quality of life.

* This study on papillomas was considered relevant for this report.
Study details are provided in appendix D (tables D-1 to D-3)

7.3 BLADDER CANCER

7.3.1 Summary of assessment-agency reviews

7.3.1.1 CEDIT

On the basis of the literature review conducted by Stables and Ash [1995], CEDIT mentions that even if PDT has obtained encouraging preliminary results for bladder cancer *in situ*, the appearance of fibroses (which cause an irreversible reduction in bladder capacity) makes it impossible to expand the use of this technique. Trials performed with 5-ALA on animals seem to indicate that this agent would be less pathogenic than Photofrin.

According to CEDIT, further randomized clinical trials are needed to validate this treatment.

7.3.1.2 ICSI

This indication is not covered in the ICSI reports.

7.3.2 Recent primary studies

Three studies meeting the inclusion criteria were selected for this report. Table 8 summarizes them according to level of evidence and study design, PDT application and authors' general conclusions. PDT is used with patients presenting with transitional cell carcinoma (TCC) of the bladder.

In the treatment of superficial recurrent TCC of the bladder, PDT (PF) obtained a complete response in 45% of patients (9 out of 20), but five of the nine patients had recurrences within six months after treatment. Twenty-five percent of the subjects experienced complications, including asymptomatic reflux; one of the five patients developed bladder contracture and fibrosis. The authors conclude that PDT is safe and effective in terms of tumour response when treatment consists of a dose of 1.5 mg/kg activated by a total laser-light dose of 2500 to 3250 J. They also state that PDT administration requires careful dosimetry and that more ample research is needed to study this point and the other aspects of the treatment [Walther et al., 1997].

Another uncontrolled trial examined the effectiveness of PDT (PF) as an alternative to cystectomy in patients with TCC that fails to respond to treatment with bacillus Calmette-Guérin (BCG) [Nseyo et al., 1998b]. A complete-response rate of 58% at three months was noted, but it dropped to 31% at twelve months. Nineteen percent of the patients had bladder contractures and 38% had to undergo cystectomy. The authors conclude that PDT (PF) is a potentially promising alternative to cystectomy in patients with TCC that is resistant to BCG therapy. These conclusions have nevertheless been criticized because the subjects may not have been resistant to BCG therapy, and the follow-up time was considered too short to allow for the numerous therapeutic failures to be detected in the first two years after treatment [Herr, 1998].

Another study examined the effects of PDT in the treatment of resistant superficial TCC. After three months of follow-up, complete- or partial-response rates were 75% for residual TCC and 84% for carcinoma *in situ* when ablative PDT was used. These rates rose to 90% when patients underwent prophylactic PDT (i.e., when PDT was used after complete resection of the tumour). Twenty-nine percent of the patients developed complications in the form of bladder contractures. In an effort to reduce the complication rate, it is recommended to offer three courses of PDT (at 0, 6 and 12 months) using a lower dose of photosensitizer (1.5 mg/kg) and a lower light intensity (15 J/cm2) [Nseyo et al., 1998a].

TABLE 8

Selected studies on the effects of PDT (PF) (bladder cancer)

LEVEL OF EVIDENCE	AUTHORS AND NUMBER OF CASES	PDT APPLICATION STUDIED	CONCLUSIONS
II-3 (case series)	Walther et al., 1997 20 cases	Treatment of recurrent superficial transitional cell carcinoma (TCC)	PDT is effective in terms of tumour response to treatment. PDT is safe but the dosimetry must be selected with care.
	Nseyo et al., 1998a 58 cases	Treatment of refractory superficial TCC in ablative or prophylactic PDT	At 3 months, high response rate to treatment with high complication rate (bladder contractures).
	Nseyo et al., 1998b 36 cases	PDT as an alternative to cystectomy for patients with refractory TCC	PDT seems to be a promising treatment and could replace cystectomy for patients with refractory TCC.

Study details are provided in Appendix E.

8 ECONOMIC ASPECTS

8.1 COST AND USE OF THE THERAPY

In its first report, ICSI estimated that PDT costs around US$6,000, compared with US$12,000 to US$15,000 for external-beam radiation and US$10,000 to US$60,000 for surgery [ICSI, 1997].

Some Japanese experts believe that the use of PDT for lung cancer is more cost-effective than the other therapies [Kato, 1998], but data supporting that opinion have yet to be confirmed.

The Canadian manufacturer of Photofrin [Axcan Pharma, 2000b] estimated the costs of lung-cancer treatment on the basis of those recorded in France (see appendix G). The company did not cite its information sources (but they are available on request). These estimates provide only certain reference points on the relative cost of this treatment in France. PDT could theoretically reduce costs if it were proven to be effective and to help prevent the need for other treatments. Nevertheless, to perform a real cost comparison, we would need to determine the actual effectiveness of PDT as well as the actual treatment costs in Québec for each specific type of lung cancer.

In Québec, the net cost per treatment is estimated to be $5,514.41. Table 9 presents the monetary value of each cost item. Given that the number of treatment sessions does not affect the cost of the apparatus, which is a fixed cost, we took into account only the cost of the optical fibres, the cost of the drug, hospital charges and doctors' fees, to estimate the net cost per session. The purchase price of the apparatus is its overall cost, which includes a set quantity of single-use optical fibres. The Diomed 630 nm, for example, is delivered with only 10 optical fibres, which severely restricts its use. The cost of the drug is the amount paid by the hospital pharmacy for the Photofrin. A patient weighing 70 kg would require two vials of 75 mg each per treatment.

The average cost of one day of hospitalization in Québec includes the costs related to nursing, diagnosis and therapy services, and hospital catering, as well as general service costs (administration, facilities operation and maintenance). Finally, physicians' fees, taken from the RAMQ's *Manuel des médecins spécialistes*, are estimated to be $65 per consultation. Two consultations are required for each phototherapy session.

TABLE 9

Monetary value of cost items

TYPES OF COSTS	TOTAL AMOUNTS (Can$)
Purchase price of apparatus	$106,335.00
Amortization over ten years	$10,633.50
Costs of optical fibres	$671.95
Cost of drug (2 vials of 75 mg each)	$3,770.00
Average hospitalization cost	$937.46
Medical specialist's fees	$130.00

8.2 COST-EFFECTIVENESS

A recent study compared PDT (PF) with the placement of stents for palliation of advanced esophageal cancer [Canto et al., 2002]. According to the abstract for this study (no detailed publication is available so far), PDT would apparently cost at least three times more than stents (median cost: US$19,754 vs US$5,806; $p = 0.0009$).

The differential cost-utility ratio for PDT compared with stent placement is very high (US$516,592 per person-year without invalidity). The authors conclude that stents are more cost-effective than PDT (PF).

8.3 BUDGETARY IMPACT OF PDT USE IN QUÉBEC

For the time being, the number of Photofrin treatments possibly offered is not quantifiable for these three types of cancer because it is impossible to estimate how many patients in the palliation stage of their illness could benefit from Photofrin-mediated PDT.

9 DISCUSSION

9.1 ESOPHAGEAL CANCER

9.1.1 Advanced cancers

Generally speaking, the results of the selected recent primary studies agree with the conclusions in both the CEDIT and the ICSI reports on photodynamic therapy, that is, PDT (PF) is both safe and effective for the treatment of advanced esophageal cancers. The preliminary results of these studies emphasize the advantage of exploring differents options, such as the use of PDT in combination with other therapies (radiotherapy, stents) and using different wavelengths according to the indication. Note that most of these primary studies are based on weak evidence and do not have control groups (level II-3, according to our grading scale).

There are, in effect, several options other than PDT for the palliative treatment of advanced esophageal cancer, including laser ablation, placement of metal stents and dilation. The last option provides only a transitory result, but it is often the first step in most other palliative measures [Lightdale, 2000]. The obligation to avoid all exposure to sun for four to six weeks after PDT could play against this palliation option, especially for patients who are expected to survive for only a few months. The treatments used vary widely throughout the world, and the question of which is the best treatment is controversial [Luketich et al., 2000; Moghissi et al., 2000]. It would therefore be relevant to compare PDT with other available treatment options, such as Nd:YAG laser ablation and expandable stents.

9.1.1.1 COMPARISON WITH ND:YAG LASER ABLATION

Although no new studies comparing the efficacy of PDT with that of Nd:YAG have been published since the ICSI and CEDIT reports, it is generally agreed in the scientific literature that both treatments offer the same comparable results overall. Some benefits of PDT have nonetheless been established. For example, it has been noted that PDT is less uncomfortable for patients [Marcon, 1994] and easier to administer, and that it is appropriate when the tumour morphology or site makes it difficult to use Nd:YAG [Sibata et al., 2001; Dougherty et al., 1998; Lightdale et al., 1995].

9.1.1.2 COMPARISON WITH EXPANDABLE STENTS

The studies comparing PDT with Nd:YAG laser treatment were produced before the advent of expandable stents, currently the most widely used treatment in the United States [Lightdale, 2000; Nishioka, 1999].

Expandable metal stents are considered by some to be the most important recent breakthrough in the palliative treatment of esophageal cancer [Ponec and Kimmey, 1997] because they offer several potential benefits [Alderson and Blazeby, 1995; Sturgess and Morris, 1995]. Stent placement is easy and can be done in all hospital centres. Stents provide immediate relief; morbidity is low; and the cost reasonable [Courtay et al., 1999]. Moreover, the use of stents could improve patients' quality of life by avoiding the inconveniences of photosensitization associated with PDT (PF) or the obligation to travel long distances to receive treatment [Narayan and Sivak, 1994].

A randomized trial (only the abstract is available) reported similar results for the two treatments [Canto et al., 2002]. However, compared with PDT, stents were found to be superior because they provided fast relief from dysphagia and were both easy to use and cost-effective [Canto et al., 2002]. Also, the high costs of Photofrin and the fact that stenting has become the most commonly used treatment in the United States [Lightdale, 2000] limit interest in using PDT for this application in Québec.

Given these results, PDT (PF) is expected to be generally used as a complementary therapy for advanced esophageal cancer (when other treatments are contraindicated), as is currently the case in the United States [Lightdale, 2000]. Over the next few years, significant improvements are expected to be made to both PDT and stents, which will have an impact on their potential use. It is important to offer patients appropriate palliative care and to take into account the benefits it may provide for patients' autonomy and home care. Finally, the treatment program adopted for a patient depends on many factors, including the equipment available, health professionals' expertise and preferences, treatment costs and patient preferences [Luketich et al., 2000].

9.1.2 Superficial cancers

PDT (PF) seems beneficial for this indication, but currently published studies offer only weak evidence to that effect. The two recent studies selected state that PDT (PF) is relatively effective for this indication, which tallies with the ICSI and CEDIT reports. Despite these promising results regarding the suppression rate of superficial lesions, there have not been enough trials including a sufficient number of subjects and comparing PDT with surgery to justify this possible indication.

9.2 LUNG CANCER

Recent studies have shown that PDT is relatively effective for the palliation of advanced cancers and especially that PDT (PF) is comparable to Nd:YAG laser ablation [Diaz-Jiménez et al., 1999]. These observations agree with the conclusions in the ICSI reports and in review articles [Chang and Bown, 1997] on the effectiveness of this treatment. Several studies have also indicated that PDT would be beneficial for treating malignant pleural mesothelioma (MPM). As for superficial cancers, no new study has come to support the ICSI conclusion that PDT is an effective treatment for tracheobronchial cancers and superficial lesions.

Although some encouraging results have been noted regarding the efficacy of PDT for lung cancers, the scientific literature offers no convincing evidence that PDT has any advantage over other complementary therapies or over surgery alone [Smith and Hahn, 2002; Pass et al., 1997]. Other interventions can be less costly, faster or safer than PDT, such as high-frequency coagulation and cryotherapy. Further studies, especially controlled trials, must be conducted before the use of PDT can be justified for these indications [Moskal et al., 1998].

9.3 BLADDER CANCER

Photodynamic therapy could be a complementary treatment for recurrent superficial transitional cell carcinoma (TCC) of the bladder (e.g., for patients who are not eligible for chemotherapy or immunotherapy). The advantage would be to avoid the need for cystectomy in patients resistant to treatment by bacillus Calmette-Guérin (BCG).

The three recent studies selected recorded encouraging, albeit highly variable, complete-response rates (from 45% to 84%), depending on the type of carcinoma and the length of follow-up. These studies also reported a high complication rate and cautioned that the dosimetry must be chosen with care. These observations resemble the conclusions reached by CEDIT and other authors [Chang and Bown, 1997], who report encouraging preliminary results mitigated by a high complication rate and the lack of randomized trials. In fact, complete-response rates from 33% to 100% were recorded in eight of the selected studies published between 1987 and 1995 [Nseyo, 1998b]. These variable rates can be explained in part by the different follow-up times in the studies (from 3 to 55 months) because a high recurrence rate was seen in the two years following the PDT treatments [Walther et al., 1997; Nseyo, 1998b; Herr, 1998].

The photosensitizer 5-ALA seems to be effective for bladder cancer because it is less pathogenic than Photofrin [Courtay et al., 1999]. Kriegmar and associates [1996] have

reported good outcomes in terms of treatment response, bladder preservation and lack of major complications.

There may be several benefits to replacing cystectomy with PDT, especially that of maintaining a better quality of life. Overall, this application of PDT should be studied much further and backed by research on its efficacy and on the optimal treatment parameters required to minimize complications: multiple courses of PDT treatment, lower doses of photosensitizing agent and less intense or shorter light activation, for example [Dougherty, 2002; Nseyo, 1998a].

9.4 BARRETT'S ESOPHAGUS: NEW INDICATION FOR PDT (PF)

Barrett's esophagus appears when esophageal epithelium is replaced by abnormal epithelium [Wang and Sampliner, 2001], which leads to a risk of developing esophageal cancer that is from 30 to 52 times greater than that for the general public [Overholt, 1999]. White men aged 50 and over, along with smokers with Barrett's esophagus, are at high risk [Spechler, 2002b]. Esophageal-tissue changes appear after prolonged gastro-esophageal reflux [Enzinger et Mayer, 2003; Spechler, 2002a], a major risk factor in esophageal cancer [Lagergren et al., 1999]. The incidence of esophageal cancer is rising in North America [Devesa et al., 1998]. This rise is possibly associated with the high prevalence of gastro-esophageal reflux, given that nearly 50% of adults in the United States present with symptoms of this disease each month [Shaheen and Ransohoff, 2002].

Esophageal carcinoma is preceded by low-grade dysplasia followed by high-grade malignancy [Hamilton, 1985]. Yet there is still a great deal of uncertainty about the natural evolution of this disease. Certain recommendations for treating Barrett's esophagus in the United States are based on an annual cancer incidence of 1% to 2% in people with that disorder [Spechler, 2002a]. Yet, it is now generally admitted that this incidence is actually 0.5% per year [Enzinger and Mayer, 2003; Spechler 2002a; Shaheen et al., 2000].

Treatment of patients with Barrett's esophagus generally involves three components: treatment of gastric reflux, endoscopic surveillance to detect dysplasia, and treatment of dysplasia [Enzinger and Mayer, 2003; Spechler 2002b]. Clinical guidelines on the treatment of this disorder have recently been published [Sampliner et al., 2002; Boyer et al., 2000; Sampliner et al., 1998]. The optimal type of treatment, however, still raises many complex questions and a good deal of uncertainty. According to U.S. recommendations, endoscopic exploration is indicated for any person with chronic gastric reflux [Sampliner et al., 2002]. This recommendation has been refuted in the systematic review conducted by Shaheen [2002], who concludes that there is not enough evidence to warrant this practice. Enzinger et Mayer [2003] also conclude that any recommendation on the endoscopic surveillance of patients with Barrett's esophagus must be supported by objective data.

The use of surgery (esophagectomy) for these patients and those with high-grade dysplasia has also recently been put into question. Esophagectomy has a high mortality rate (3–12%) and a high complication rate (30–50%) [Swisher et al., 2000]. A recent study observed that in patients diagnosed with Barrett's esophagus, surgery did not prolong survival more than endoscopic surveillance. This procedure is recognized as an alternative treatment to surgery, especially in healthy people aged 50 and over [Spechler, 2002a].

An increase in the incidence of esophageal cancer and the high complication rate from surgery are inciting researchers to develop new endoscopic treatments. These ablative techniques are thermal, chemical or mechanical [Van den Boogert et al., 2000] and destroy abnormal tissue to allow for the regrowth of normal epithelium [Wang and Sampliner, 2001].

In the conclusions of the first ICSI report, the authors mention that Barrett's esophagus "responds to PDT" on the basis of three case

series studied by the same research group [Overholt and Panjehpour, 1996a; Overholt and Panjehpour, 1995a; Overholt and Panjehpour, 1995b]. Similarly, the CEDIT report mentions that this indication for PDT is of potential interest also on the basis of publications by these same authors [Overholt and Panjehpour, 1996a; Overholt and Panjehpour, 1996b]. Studies presenting similar results (from case series) for this PDT application have been published more recently [Overholt and Panjehpour, 2000; Panjehpour et al., 2000; Overholt et al., 1999], the second and third of which are included in ISCI's update [2002]. In addition, Étienne and associates [2000] obtained encouraging results from the use of PDT with temoporfin (Foscan®/mTHPC) in the treatment of Barrett's esophagus.

A randomized trial comparing the use of PDT (PF) combined with omeprazole and the use of omeprazole alone to treat high-grade dysplasia in cases of Barrett's esophagus is currently underway [Axcan Pharma, 2003]. Preliminary results report a significant reduction in dysplasia and a lower cancer rate in the group treated with PDT (PF) [Axcan Pharma, 2003]. Full results from this study will provide valuable information on this potential indication for PDT. Several key questions should be examined, such as the long-term efficacy of PDT, its complications and the potential persistence of dysplasia sites or deep carcinoma [Spechler, 2002b].

Photofrin has recently been approved in Canada for photodynamic therapy of high-grade dysplasia associated with Barrett's esophagus [Axcan Pharma, 2003]. This potential indication has sparked a great deal of interest because it is attractive on a theoretical level and affects a large number of eligible patients.

This new situation could initially lead to requests for this therapy for patients who are not candidates for surgery. It is also expected that a certain number of patients will prefer PDT to surgery or endoscopic surveillance. This would have a major impact on Québec's health system, given the large number of patients to be treated. As a result, hospital budgets will be seriously affected because hospitals will need to have staff on board with the required specialized training and will need to buy the equipment used to administer PDT.

9.5 GENERAL CONSIDERATIONS

Like the studies on esophageal cancer, those that examined the treatment of lung cancer have often involved multiple courses of PDT with up to three doses of photosensitizing agent and six laser-light doses [Diaz-Jiménez et al., 1999; Moghissi et al., 1999; McCaughan, 1999; Shikowitz et al., 1998]. But PDT could also be combined with several other available treatments, depending on the indication.

The new photosensitizers would apparently have advantages over Photofrin because they generally produce more singlet oxygen, clear from the body more rapidly and cause fewer skin-photosensitivity reactions. However, there is no information on the potential cost of these agents. These innovations and other technological advances are expected to improve PDT outcomes [Ninane, 1999].

The new photosensitizers and laser treatments under development are liable to require light sources with longer wavelengths. It would therefore be logical to invest in light sources capable of emitting different wavelengths (such as the pumped-dye laser), which would allow for the administration of several types of treatment [CORD, 2001].

10 CONCLUSIONS AND RECOMMENDATIONS

Analysis of the body of information currently available on PDT (PF) for the treatment of esophageal, lung and bladder cancers leads to the following conclusions and recommendations concerning the place of PDT (PF) in Québec's therapeutic arsenal.

- With respect to **lung and bladder cancers, and superficial esophageal cancers**, findings seem to indicate that PDT (PF) has a therapeutic effect, but there is not enough evidence to conclude that it has any comparable advantage over other available treatments.

  For the treatment of lung and bladder cancers and superficial esophageal cancers, AETMIS recommends that PDT (PF) be used only for clinical research purposes and not be authorized for public coverage.

- With respect to the palliative treatment of **advanced esophageal cancer**, available studies seem to show, with only fair evidence, that the efficacy of PDT (PF) is analogous to that of other palliative treatments (Nd:Yag laser ablation, metal stents). However, treatment with PDT (PF) would apparently cost much more than that with stents. This important factor, coupled with the fact that stents are easy to use and already in widespread use, diminishes any interest there might be in using PDT (PF) for this indication and the probability that it will adopted in the current context. Nevertheless, PDT (PF) could be used as a complementary therapy when other treatments are contraindicated.

  For the palliative treatment of advanced esophageal cancer, AETMIS recommends that PDT (PF) be considered a possible option when recognized treatments are contraindicated and that PDT should undergo further clinical research.

- The recent approval of PDT (PF) in Canada for a new indication—**Barrett's esophagus**—raises important issues. A more in-depth examination will need to be conducted of the long-term efficacy of PDT for this indication and of its place in the current therapeutic arsenal, which already offers several treatment options. These issues should preferably be reviewed in a separate assessment report.

  For the treatment of Barrett's esophagus, AETMIS recommends that PDT (PF) be fully assessed before it is introduced into current practice.

- Finally, there seems to be a near consensus in all the literature reviewed that the field of application of PDT will expand and undergo many technological developments, especially with respect to the photosensitizing agents used, which may lead to greater reliance on this therapy in the years to come. Photodynamic therapy is not expected to replace surgery, radiotherapy or chemotherapy; rather, it is meant to complement them [Chang and Bown, 1997]. Still, we will need to obtain stronger scientific evidence of the advantages of PDT over other treatments and to examine its impact on the Québec health-care system before its use can be justified for these new applications.

  AETMIS recommends that a technology watch be implemented to track technological advances in PDT in general and its new applications in particular.

APPENDIX A

ICSI SCHEME FOR GRADING SCIENTIFIC EVIDENCE

Evidence is graded according to the following system:

Grade A
Conclusion based on a randomized, controlled trial that has been published in a peer-reviewed journal.

Grade B
Conclusion based on a well-designed study published in a peer-reviewed journal (but not on a randomized, controlled trial), such as:

- a trial using historical or other non-randomized controls;
- a prospective cohort study;
- a case-control study; or
- a meta-analytic study.

Grade C
Conclusion based on one of the following (but not on any studies of the types mentioned above):

- uncontrolled case series; or
- expert opinion.

Position statements, panel consensus statements from the National Institutes of Health (NIH) or elsewhere, review articles or textbook chapters that cite primary evidence are not assigned a grade because they are not primary evidence. The individual studies cited in such secondary sources can be graded according to the categories presented above.

Source: ICSI, 1997.

APPENDIX B

GRADING SCHEME FOR LEVELS OF EVIDENCE USED BY THE *CONSEIL QUÉBECOIS DE LUTTE CONTRE LE CANCER* (CQLC)

This grading scheme is used by the CQLC as well as by the European Society of Medical Oncology (ESMO) [2002] and the American Society for Clinical Oncology (ASCO) [1997].

LEVELS OF EVIDENCE AND RECOMMENDATION CATEGORIES
(according to ASCO Guidelines)

LEVEL	TYPE OF EVIDENCE
I	Evidence is obtained from meta-analysis of multiple, well-designed, controlled studies. Randomized trials with low false-positive and low false-negative errors (high power).
II	Evidence is obtained from at least one well-designed experimental study. Randomized trials with low false-positive and low false-negative errors (low power).
III	Evidence is obtained from well-designed, quasi-experimental studies such as non-randomized, controlled single-group, pre-post, cohort, time, or matched case-control series.
IV	Evidence is obtained from well-designed, non-experimental studies such as comparative and correlational descriptive and case studies.
V	Evidence from case reports and clinical examples.

GRADING OF RECOMMENDATION

GRADE	GRADING OF RECOMMENDATION
A	There is evidence of type I or consistent findings from multiple studies of types II, III, or IV.
B	There is evidence of type II, III, or IV and findings are generally consistent.
C	There is evidence of type II, III, or IV but findings are inconsistent.
D	There is little or no systematic empirical evidence.

Source: European Society of Medical Oncology (ESMO), 2002

APPENDIX C

DETAILS OF SELECTED PRIMARY STUDIES ON ESOPHAGEAL CANCER

TABLE C-1

Characteristics of randomized controlled trials published between 1997 and 2003 on esophageal cancer

AUTHORS (country)	STUDY OBJECTIVE	NUMBER OF PATIENTS, TREATMENT AND FOLLOW-UP	PATHOLOGICAL STAGES (cell types)	TYPE OF APPARATUS AND PRODUCT USED (intensity)	RESULTS	CONCLUSIONS	COMMENTS	LEVEL OF EVIDENCE
Canto et al., 2002 (United States)	To compare PDT (PF) with stents for palliation of advanced esophageal cancers.	56 patients Follow-up time not specified	Recurrent, persistent, inoperable cancer and/or metastatic cancer of the esophagus or esophagogastric junction	N/A	No survival difference between PDT and stents. 17% of patients who failed to respond to PDT were reassigned to the group treated with stents. Significant reduction of dysphagia with both treatments. Significant reduction in quality of life in group with stents but not in group treated with PDT. Several complications with both treatments. PDT cost over three times more than stents (US$19,754 vs $5,806).	PDT (PF) and stents achieved comparable results for the treatment of dysphagia. Reduction of dysphagia is nevertheless faster with stents and fewer reinterventions are required. Stents are more cost-effective than PDT (PF).	Given that only the abstract of this study is available and that relevant data on the study design are not mentioned, it is not possible to assess the scientific quality of this study or the validity of its results.	I

TABLE C-2

Characteristics of non-randomized controlled trials published between 1997 and 2003 on esophageal cancer

AUTHORS (country)	STUDY OBJECTIVE	NUMBER OF PATIENTS, TREATMENT AND FOLLOW-UP	PATHOLOGICAL STAGES	CELL TYPES	TYPE OF APPARATUS AND PRODUCT USED (intensity)	RESULTS	CONCLUSIONS	COMMENTS	LEVEL OF EVIDENCE
Mlkvy et al., 1998 (Great Britain)	To evaluate the effects of PDT (PF) on all types of gastro-intestinal tumours	22 patients: EG1 = 4 received PDT (PF) (only 1 with esophageal cancer and 3 with duodenal cancer) EG2 = 2 received mTHPc (with colorectal cancer) EG3 = 16 received PDT (5-ALA): 6 with colorectal cancer, 7 with duodenal cancer and 3 with esophageal cancer Follow-up time not specified	Not specified	Carcinomas and adeno-carcinomas	1) Metal-vapour laser PDT (PF) 2) Vapour laser PDT (mTHPc) 3) Vapour laser DPT (5-ALA) Respective intensities: 1) 628 nm (PF: 2 mg/kg) 2) 650 nm (mTHPc: 0.15 mg/kg) 3) 628 nm (5-ALA: 60 mg/kg)	One month after treatment: 67% reduction in size of esophageal tumour For all disorders treated with PDT (PF): • short-term (3 days): whitish superficial necrosis • long term (1 month +): 40–70% reduction in tumour size Complications: photosensitivity in 4 subjects	PDT (PF) is an ideal treatment for small tumours because it prevents the need for surgery Results with 5-ALA are encouraging if significant changes are made to the dosimetry	This trial had several novel aspects. Given that only 1 patient with esophageal cancer was treated with PDT, it is not possible to draw conclusions. No economic data	II-2

EG: experimental group; PDT: photodynamic therapy; PF: Photofrin; mTHPc: meta-tetrahydroxyphenyl chlorin; 5-ALA: 5-aluminolevulinic acid

TABLE C-3

Characteristics of other studies published between 1997 and 2003 on esophageal cancer

AUTHORS (country)	STUDY OBJECTIVE	NUMBER OF PATIENTS, TREATMENT AND FOLLOW-UP	PATHOLOGICAL STAGES	CELL TYPES	TYPE OF APPARATUS AND PRODUCT USED (intensity)	RESULTS	CONCLUSIONS	COMMENTS	LEVEL OF EVIDENCE
Litle et al., 2003 (United States)	To evaluate the therapeutic efficacy of PDT (PF) for the palliative treatment of patients presenting with bleeding or obstructing esophageal cancer.	215 patients All treated with Photofrin Follow-up time not specified	*Stages of dysphagia* Stage 1 = asymptomatic Stage 2 = difficulty swallowing solid food but not semi-solid food Stage 3 = difficulty swallowing solid food but not liquids Stage 4 = difficulty swallowing liquids Stage 5 = difficulty swallowing all nutriments, even saliva	Squamous cell (EG1 = 33) Adenocarcinomas (EG2 = 179) Undifferentiated carcinomas (EG3 = 3)	Tunable-dye laser PDT (PF): 2 mg/kg (630 nm)	After treatment: 85% of treatments improved the dysphagia score by at least one level ($p < 0.05$) Complications: esophageal stenoses (1.6 %), *Candida* esophagitis (1.6 %), pleural effusions (3.5 %), aspiration pneumonia (1.3 %), perforations (1.6 %) and sunburn (6.0 %) Median survival was 4.8 months. Procedure-related mortality rate was 1.8%	PDT (PF) is a safe and effective treatment for the palliation of obstructing and/or bleeding esophageal cancer. Reinterventions may be required to maintain palliative relief from dysphagia in patients surviving more than two years, and a multimodality approach, including PDT, is common.	This study deals with the best conditions for PDT use combined with other available options for symptomatic palliation of esophageal cancer.	II-3
Luketich et al., 2000 (United States)	To evaluate the therapeutic efficacy of PDT (PF) for inoperable patients at the palliative stage.	77 patients All treated with Photofrin Follow-up time not specified	*Stages of dysphagia* Stage 1 = asymptomatic Stage 2 = difficulty swallowing solid food but not semi-solid food Stage 3 = difficulty swallowing solid food but not liquids Stage 4 = difficulty swallowing liquids Stage 5 = difficulty swallowing all nutriments, even saliva	Squamous cell (EG1 = 13) Adenocarcinomas (EG2 = 64)	Tunable-dye laser PDT (PF): 1.5 to 2 mg/kg (630 nm)	After treatment: At 4 weeks, dysphagia score improved from 3.2 ± 0.7 to 1.9 ± 0.8 (i.e., 90.8 % of patients, $p < 0.05$) 7 metal stents were placed after failure of PDT (PF) Mean dysphagia-free interval = 80.3 ± 0.58. Median survival was 5.9 months. Complications: esophageal stenoses (4.8%), *Candida* esophagitis (3.2%), pleural effusions (3.2%), and sunburn (10.0%)	PDT (PF) is a safe and effective treatment for palliation of obstructing and/or bleeding esophageal cancer. Additional studies will be required to examine the cost-effectiveness of this treatment and its relative contribution to quality of life compared with other palliative options.	Presumed advantages of PDT (PF) over Nd:YAG are not supported by objective data. No economic data.	II-3

Characteristics of other studies published between 1997 and 2003 on esophageal cancer (cont'd)

AUTHORS (country)	STUDY OBJECTIVE	NUMBER OF PATIENTS, TREATMENT AND FOLLOW-UP	PATHOLOGICAL STAGES	CELL TYPES	TYPE OF APPARATUS AND PRODUCT USED (intensity)	RESULTS	CONCLUSIONS	COMMENTS	LEVEL OF EVIDENCE
Moghissi et al., 2000 (Great Britain)	To evaluate the palliative role of PDT (PF) in patients with advanced and inoperable esophageal cancer	65 patients Follow-up: up to 30 months	TNM classification of malignant tumours (see appendix F, table F-1)	Adenocarcinomas	Copper-metal vapour laser PDT (PF): 2 mg/kg (630 nm)	Dysphagia stages *before treatment* EG1 = 5, stages 0 and 1 EG2 = 13, stage 2 EG3 = 27, stage 3 EG4 = 20, stage 4 Dysphasia stages *from 6 to 8 months after treatment* EG1 = 33, stages 0 and 1 EG2 = 27, stage 2 EG3 = 5, stage 3 EG4 = 0, stage 4 Loss of 6 kg body weight and hematemesis (vomiting of blood) in 61 subjects Mean survival: deceased patients (58): 7.7 ± 0.8 months living patients (7): 16 months (2 to 30 months) Complications: stenoses and chest pain, photosensitivity (mild skin photosensitivity reaction)	PDT (PF) is a safe and effective treatment for the palliation of inoperable dysphagia in esophageal cancer. Regression in the stages of dysphagia was observed for all patients, no lesions caused by chemotherapy or radiotherapy. PDT (PF) has the potential to prolong survival in patients with less advanced or early-stage tumours.	Other patients required metal stents. No economic data.	II-3
Scheider et al., 1997 (Canada)	To evaluate PDT (PF) in patients who had previously received metal stents	4 inoperable patients with stents (Ultraflex®) treated with PDT (PF) Follow-up time not specified	*Stages of dysphagia* Stage 0 = swallows normally Stage 1 = swallows solid food Stage 2 = swallows solid and pureed food Stage 4 = swallows only liquids Stage 5 = unable to swallow liquids	Adenocarcinomas	Unspecified laser PDT (PF): 2 mg/kg (630 nm)	*Before treatment* Mean stage of dysphagia: 2.25 (2, 2, 2, 4) *6 months after treatment*: Mean stage of dysphagia: 0.25 (0, 0, 0, 1) Mean dysphagia-free interval was 92.75 days (84, 157, 76, 54). Mean survival was 254 days for three deceased patients (84, 404, 275); one patient was still alive. There were no major complications.	PDT (PF) is effective and safe to treat malignant tumour ingrowth through esophageal stents.	Small number of subjects. No economic data.	II-3

Characteristics of other studies published between 1997 and 2003 on esophageal cancer (cont'd)

AUTHORS (country)	STUDY OBJECTIVE	NUMBER OF PATIENTS, TREATMENT AND FOLLOW-UP	PATHOLOGICAL STAGES	CELL TYPES	TYPE OF APPARATUS AND PRODUCT USED (intensity)	RESULTS	CONCLUSIONS	COMMENTS	LEVEL OF EVIDENCE
Grosjean et al., 1998 (Switzerland)	To evaluate 514 nm compared with 630 nm light irradiation in the treatment of superficial cancers of the esophagus and bronchi	15 patients with carcinomas treated with Photofrin 514 nm: EG1 = 5 (1 patient with bronchial cancer and 4 patients with esophageal cancer) 630 nm: EG2 = 10 (3 patients with bronchial cancer and 7 with esophageal cancer) 8 bronchial tumours and 14 esophageal tumours identified 9 tumours treated with PDT (PF) at 514 nm 13 tumours treated with PDT (PF) at 630 nm Follow-up time: 21 months (from 6 to 49)	IIIA, IIIB, IV and others (not defined)	Carcinomas and adeno-carcinomas	Pumped-dye laser PDT (PF): 2 mg/kg (514 nm and 630 nm)	Complete response after 3 months of treatment: With 630 nm: 9 out of 13 esophageal tumours (69%) With 514 nm: 6 out of 9 superficial tumours (67%) Complications (3 cases): pleural effusion, fever, chest pain, edema and erythemas	PDT (PF) used with a 514-nm wavelength can cure superficial esophageal and bronchial cancers. These probabilities of success are analogous to those obtained with 630 nm. In the case of esophagal carcinomas, a 514-nm wavelength prevents deep-tissue damage and therefore reduces the risk of tissue perforation.	The small sample size does not allow us to draw conclusions. No economic data.	II-3

TABLE C-4

Characteristics of other studies on esophageal cancer published between 1997 and 2003, using hematoporphyrin derivatives other than Photofrin

AUTHORS (country)	STUDY OBJECTIVE	NUMBER OF PATIENTS, TREATMENT AND FOLLOW-UP	PATHOLOGICAL STAGES	CELL TYPES	TYPE OF APPARATUS AND PRODUCT USED (intensity)	RESULTS	CONCLUSIONS	COMMENTS	LEVEL OF EVIDENCE
Maier et al., 2001a Maier et al., 2001b (Austria)	To compare HpD/ Photosan with 5-ALA to treat advanced carcinomas.	49 patients 22 treated with 5-ALA 27 treated with HpD/Photosan Follow-up time not specified		Advanced esophageal carcinomas	KTP-Nd:YAG laser PDT (HpD): 2 mg/kg (630 nm) PDT (5-ALA): 60 mg/kg	Reduction of dysphagia, stenosis diameter and tumour length with both treatments and at one-month follow-up; statistically significant difference in favour of PDT. No sunburns or other treatment-related major complications were observed in either group.	Despite the limitations of a non-randomized trial, HpD/Photosan seems to be superior to 5-ALA for the treatment of advanced esophageal carcinomas.	The same study was published in two scientific journals (*see* References).	II-3
Maier et al., 2000 (Austria)	To compare PDT combined with radiotherapy and radiotherapy alone.	119 patients 21 patients: dilation and ablation with Nd:YAG before therapy. 44 patients received PDT (HpD) followed by brachytherapy. 75 patients refused PDT and received brachytherapy alone. Follow-up time not specified	TNM classification (appendix F, table F-1): Stage III: 80 patients Stage IV: 39 patients T3 = 46 T4 = 73 N1 = 65 NX = 54 M0 = 80 M1 = 39	Advanced esophageal carcinomas	Nd:YAG laser HpD/hematoporphyrin polyester: 2 mg/kg (630 nm)	3 months after treatment: Reduction of stenosis and dysphagia, and increased survival; statistically significant difference in favour of PDT. Major complications: 11 (9.2%); statistics are not differentiated by group.	PDT followed by radiotherapy is effective in palliating advanced esophageal cancers. Patients must be selected with care to prevent major complications.	Patients in control group did not want to receive PDT (PF) even if they met inclusion criteria.	II-3
Corti et al., 2000 (Italy)	To evaluate the effects of PDT combined with radiotherapy (RT) in inoperable patients.	62 subjects 54 patients inoperable for medical reasons and 8 for other reasons. Same patients were treated twice: 1) PDT alone, and 2) PDT + RT in cases of partial or unsatisfactory response after two PDT sessions. Median overall survival: 32 months (from 3 to 90)	IIB, IIIA, IIIB	Adenocarcinomas and squamous cell	Argon-dye laser PDT (HpD): 5 mg/kg (630 nm)	Response rate: PDT alone: Complete: 37% Partial: 48% Unsatisfactory: 15% PDT with adjuvant radiotherapy: Complete: 82% Partial: 15% Unsatisfactory: 3% PDT alone with complete response (23 patients): Median overall survival: 50 months Median overall survival without recurrence: 68 months Complications: Toxicity: 3 cases of esophageal stenosis (7%) and 1 case of tracheobronchial fistula (2.5%) after PDT (HpD + RT)	PDT (PF) is an effective treatment for esophageal cancer. Adjuvant radiotherapy in cases of incomplete response to PDT is effective and potentially curative.	Statistics on complete, partial and minimal responses and median survival are difficult to interpret with the addition of radiotherapy. No economic data.	II-3

APPENDIX D

DETAILS OF SELECTED PRIMARY STUDIES ON LUNG CANCER

TABLE D-1

Characteristics of randomized controlled trials published between 1997 and 2003 on lung cancer

AUTHORS (country)	STUDY OBJECTIVE	NUMBER OF PATIENTS, TREATMENT AND FOLLOW-UP	PATHOLOGICAL STAGES (cell types)	TYPE OF APPARATUS AND PRODUCT USED (intensity)	RESULTS	CONCLUSIONS	COMMENTS	LEVEL OF EVIDENCE
Diaz-Jiménez et al., 1999 (Spain)	To evaluate the therapeutic efficacy and safety of PDT (PF) compared with Nd:YAG laser ablation	31 inoperable patients with partial or complete tracheobronchial obstructions EG1 = 14 subjects treated with PDT (PF) EG2 = 17 subjects treated with Nd:YAG Follow-up time: 24 months	I, II, IIIA, IIIB, IV (small-cell adenocarcinomas and squamous cell)	Argon-pumped dye laser PDT (PF): 2 mg/kg (630 nm) Nd:YAG (15 to 80 watts)	*Before treatment* (EG1/EG2) I = 3/1 II = 1/0 IIIa = 2/4 IIIb = 3/7 IV = 3/4 Recurrences: 2/1 *After treatment* (EG1 vs EG2) Response one week after treatment: 43% vs 53% (p = ns) Response one month after treatment: 38.5% vs 23.5% (p = ns) Survival: 265 vs 95 days (p = 0.007) Similar symptomatic relief in both groups Complications: photosensitivity, bronchitis, cough and dyspnea One death probably linked to PDT (PF)	PDT (PF) is a valid palliative treatment for lung cancer (small-cell adenocarcinomas). Both techniques are similar in terms of efficacy and safety.	Nd:YAG laser is not approved in Canada. Stages are not compared. This study shows that Photofrin has a modest palliative effect. Shortcoming: small sample size. No economic data.	I
Pass et al., 1997 (United States)	To evaluate the efficacy of PDT (PF) combined with surgery compared with post-operative immuno-chemotherapy for malignant pleural mesotheliomas.	63 patients, including 48 who were randomized EG1 = 25, PDT (PF) with surgery EG2 = 23, surgery without PDT (PF) 15 patients were withdrawn from the trial because their tumours could not be debulked to a maximum of 5 mm. Median follow-up (of treatment under analysis): 23.1 months	Malignant pleural mesothelioma (all, but not staged before treatment) Post-operative staging of EG1/EG2: Stage I = 2/2 Stages IIA and IIB = 2/2 Stages IIIA and IIIB = 21/17 Stages IV = 0/2	Coherent pumped-dye laser PDT (PF): 2mg/kg + surgery (630 nm for PDT) Surgery without PDT (PF)	Median survival with recurrence: EG1 = 14.1 months EG2= 14.4 months (p = ns) Median survival without recurrence: EG1 = 8.5 months EG2 = 7.7 months (p = ns) Mean survival of 15 withdrawn patients: 7.2 months 1 death in EG1 related to PDT (PF II) No difference in the number or gravity of complications related to surgery or immunochemotherapy Each group had two bronchopleural fistulas.	Combining PDT (using first-generation photosensitizers) with surgery and immunotherapy offers no benefit in terms of survival or local necroses.	Toxicity and complications remained comparable in EG1 and EG2. Insufficient number of subjects in each group. No economic data.	I

p = ns: non-significant probability

TABLE D-2

Characteristics of non-randomized controlled trials published between 1997 and 2003 on lung cancer

AUTHORS (country)	STUDY OBJECTIVE	NUMBER OF PATIENTS, TREATMENT AND FOLLOW-UP	PATHOLOGICAL STAGES (cell types)	TYPE OF APPARATUS AND PRODUCT USED (intensity)	RESULTS	CONCLUSIONS	COMMENTS	LEVEL OF EVIDENCE
Shikowitz et al., 1998 (United States)	To verify the efficacy of Photofrin for respiratory papillomatosis	81 patients EG = 48 subjects treated with PDT (PF) EG1 = 24 (3.25 mg/kg of Photofrin) EG2 = 24 (4.25 mg/kg of Photofrin) CG = 33 (unspecified treatment, but refusal of PDT [PF]) Follow-up time not specified	Not specified (all)	Tunable argon-pumped dye laser for PDT (PF) CO_2 laser (630 nm)	*Before treatment* Median papilloma growth rates: • EG1 = 0.143 (23 patients) • EG2 = 0.563 (16 patients) • CG = 0.113 (22 patients) *1 year after treatment* Median papilloma growth rates: • EG1 = 0.124 • EG2 = 0.177 • CG = 0.071 In the first year, the proportion of patients who experienced a decrease in recurrence rate greater than 50% was higher in the treated group than in the control group. Three-year follow-up confirmed that improvement was maintained for subset of EG2 patients and according to figures from other studies. No mention of side effects.	Reduction of pulmonary papillomas with PDT (PF) (4.25 mg/kg). PDT (PF) modifies recurrence rates but does not completely dispel latent persistence of human papillovirus (HPV) DNA. Very promising treatment.	Control-group treatments were not specified. Patients in control group did not want to receive PDT (PF) even if they met inclusion criteria. Difficult to interpret overall results. No economic data.	II-2

EG: experimental group; CG: control group.

TABLE D-3

Characteristics of studies on lung cancer published between 1997 and 2003 with evidence from multiple-time series or multicentre trials

AUTHORS (country)	STUDY OBJECTIVE	NUMBER OF PATIENTS, TREATMENT AND FOLLOW-UP	PATHOLOGICAL STAGES (cell types)	TYPE OF APPARATUS AND PRODUCT USED (intensity)	RESULTS	CONCLUSIONS	COMMENTS	LEVEL OF EVIDENCE
Moskal et al., 1998 (United States)	To evaluate the efficacy of adjuvant PDT (PF) combined with surgery for malignant pleural mesotheliomas.	40 patients PDT (PF) after surgical resection Follow-up time not specified	I, II, III and IV (TNM classification, appendix F, table F-2) Grades II and III comprise (IIA + IIB) and (IIIA + IIIB) Post-operative classification: Stage I = 12 patients Stage II = 1 patient Stage III = 25 patients Stage IV: 2 patients (All) Carcinomas = 25 Sarcomas = 5 Both = 10	Surgery Argon-pumped dye laser for PDT (PF): 2mg/kg (630 nm)	Median two-year survival rate: • All patients = 15 months • Stages I and II = 36 months • Stages III and IV = 10 months Estimated 2-year survival rates: • All patients = 23% • Stages I and II = 61% • Stages III and IV = 0% Complications in 18 patients (45%): respiratory insufficiency, septicemia, atrial fibrillation, bronchopleural fistula; 5 subsequent operations.	PDT (PF) and surgery obtain good survival results in stages I and II. For stages III and IV, further investigation is required to find better treatment modalities. Improvements in early detection and pre-operative staging are necessary for proper selection of patients liable to benefit from the treatment.	Comparative data not provided. No economic data.	II-3
Moghissi et al., 1999 (Great Britain)	To evaluate the efficacy of PDT (PF) for symptom palliation in patients with inoperable lung cancer To determine survival benefit.	100 patients with inoperable (advanced) cancers treated with PDT (PF) alone Follow-up time not specified	IIIA, IIIB and IV Stage IIIA = 73 patients Stage IIIB = 17 patients Stage IV = 10 patients (90% squamous cell and 10% small-cell adenocarcinomas)	Copper laser for PDT (PF): 2mg/kg (630 nm)	From 6 to 8 months after treatment: Pulmonary obstruction: • Before = 85.8% • After = 17.5% Mean forced vital capacity: • Before = 2.07 ± 0.78 L • After = 2.50 ± 0.74 L Forced expiratory volume: • Before = 1.38 ± 0.56 L • After = 1.66 ± 0.57 L Overall 2-year survival: 19% • 10 patients alive (mean survival was 36 months and median survival was 29 months) • 90 patients died (mean survival was 9 months and median survival was 5 months)	PDT (PF) is effective for palliation of inoperable advanced lung cancer. Patients who had a WHO Performance Status greater than 2 had added survival benefit.	Additional randomized trials are necessary to validate this PDT application. Economic aspects are not examined.	II-3

APPENDIX E

DETAILS OF PRIMARY STUDIES ON BLADDER CANCER

TABLE E-1

Characteristics of studies on bladder cancer published between 1997 and 2003 with evidence from multiple-time series or multicentre trials

AUTHORS (country)	STUDY OBJECTIVE	NUMBER OF PATIENTS, TREATMENT AND FOLLOW-UP	PATHOLOGICAL STAGES (cell types)	TYPE OF APPARATUS AND PRODUCT USED (intensity)	RESULTS	CONCLUSIONS	COMMENTS	LEVEL OF EVIDENCE
Walther et al., 1997 (United States)	To verify the therapeutic efficacy of PDT (PF) in the treatment of superficial transitional cell carcinoma (TCC).	20 patients resistant to treatment with bacillus Calmette-Guérin, mitomycin, thiotepa and/or doxorubicin Treated with PDT (PF) alone Follow-up time from 3 to 56 months	0a and 1 (appendix F, table F-3) Carcinomas, TCC, carcinoma *in situ* (Cis)	Coherent Innova 200 Argon Ion Laser System for PDT (PF): 1.5 or 2 mg/kg (630 nm)	3 months after treatment: • 45% complete response (9 out of 20 patients). Four of the nine patients remained without recurrent disease during follow-up time, which varied between 23 and 59 months. • 80% (16 of 20 patients) experienced recurrences and 8 of 16 underwent cystectomies. Complications: symptomatic vesicoureteric reflux (more frequent at higher doses), transitory acute bladder-wall irritation, other minor problems.	PDT (PF) with a dose of 1.5 mg/kg activated by a total light dose of 2500 to 3000 J is a safe treatment that resulted in tumour response. It would be beneficial to examine the response differences in TCC and Cis cancer cells, according to PDT doses. An in-depth analysis of dosimetry is desirable. This treatment seems promising for bladder cancer.	Phase I trial is non-conclusive. No comparisons with another group. Only 4 of 20 patients had complete responses, but at different follow-up times. No economic data.	II-3
Nseyo et al., 1998a (United States)	To evaluate the therapeutic efficacy of PDT (PF) in patients with recurrent disease (TCC and Cis) after standard treatments (chemotherapy with bacillus Calmette-Guérin [BCG] and transurethral resection).	58 patients 39 patients underwent ablative PDT 19 patients underwent prophylactic PDT (after complete resection of the tumour) Median survival 50 months (from 9 to 110).	Ta = 24 patients T1 = 14 patients Cis = 20 patients	Argon-dye laser PDT (PF): 1.5 or 2 mg/kg (630 nm)	Complete or partial response rates observed 3 months after treatment: *Ablative PDT* • 84% in the 19 subjects with residual resistant papillary TCC. • 75% in the 20 subjects with refractory Cis. *Prophylactic PDT* • 90 %. Survival (all patients): At 50 months, 59% (34/58) were still alive and 31 had had no recurrence. Projected five-year survival rate 45%. Mortality: 24 deaths among 58 patients. Complications: photosensitivity in 22% of patients, bladder contractures in 39% and 0% in subjects who received 2.0 and 1.5 mg/kg, respectively.	PDT (PF) with a dose of 1.5 mg/kg activated by a light dose of 15 J/cm^2 should be considered a safe treatment for refractory Cis and TCC.	Study outcomes are not conclusive because there was no control group. Randomized controlled trials would be required. No economic data.	II-3

Characteristics of studies on bladder cancer published between 1997 and 2003 with evidence from multiple-time series or multicentre trials (cont'd)

AUTHORS (country)	STUDY OBJECTIVE	NUMBER OF PATIENTS, TREATMENT AND FOLLOW-UP	PATHOLOGICAL STAGES (cell types)	TYPE OF APPARATUS AND PRODUCT USED (intensity)	RESULTS	CONCLUSIONS	COMMENTS	LEVEL OF EVIDENCE
Nseyo et al., 1998b (United States)	To verify the therapeutic efficacy of PDT (PF) as an alternative to cystectomy after failure of BCG therapy.	36 patients After failure of BCG therapy Follow-up time not specified	0a, 0is and I (appendix F, table F-3) Carcinoma *in situ*	Argon-pumped laser for PDT (PF): 2 mg/kg (630 nm)	*Before treatment:* All selected patients had recurrent cancer (stages were not specified) *3 months after treatment:* ▪ 58% complete response (21 patients) ▪ 42% incomplete response (15 patients) *12 months after treatment:* ▪ 31% without recurrence (11 patients); median survival of 12 months (9 to 48) ▪ 28% with recurrence (10 patients) Complications: ▪ Cystectomy owing to persistent carcinomas: 14 patients (38%) ▪ Bladder contractures at 12 months or more: 7 of 36 patients (19.4%) ▪ Photosensitivity: 11 patients (31%) ▪ Incontinence, spasms, dysuria and pubic pain	PDT seems to be a promising treatment and alternative to cystectomy for patients with refractory carcinoma *in situ*. Adverse effects caused by photosensitivity limit its therapeutic efficacy.	The trial involved only patients with recurrences. PDT (PF) is suggested for refractory cases (carcinoma *in situ*). No control group. Economic aspects are not examined.	II-3

APPENDIX F

TNM CLASSIFICATION FOR MALIGNANT TUMORS

TABLE F-1

TNM classification of esophageal cancer stages

PATHOLOGICAL STAGES	PRIMARY TUMOR	REGIONAL LYMPH NODES	DISTANT METASTASIS
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
	T3	N0	M0
Stage IIB	T1*	N1	M0
	T2	N1	M0
Stage III	T3	N1	M0
	T4	Multiple N	M0
Stage IV subdivided into:	Multiple T	Multiple N	M1
Stage IVA	Multiple T	Multiple N	M1a
Stage IVB	Multiple T	Multiple N	M1b

Source: International Union Against Cancer (2002)

Legend

T = Primary tumor

TX = Cannot be assessed
T0 = No evidence of primary tumour
Tis = Carcinoma *in situ*
T1 = Tumor invades submucosa*
T2 = Tumor invades muscle tissue
T3 = Tumor invades adventitia*
T4 = Tumor invades adjacent tissue structures

N = Regional lymph nodes

NX = Regional lymph nodes cannot be assessed
N0 = No regional lymph node metastasis
N1 = Metastasis in regional lymph nodes

M = Distant metastasis in regions other than in lymph nodes

MX = Distant metastasis cannot be assessed
M0 = No distant metastasis
M1 = Distant metastasis
M1a = Metastasis in cervical nodes and celiac lymph nodes (according to tumour seat in esophageal tract)
M1b = Other types of distant metastasis

*T1 is subdivided into T1m and T1sm: T1m for cancer confined to mucosa, and T1sm for cancer invading submucosa

TABLE F-2

TNM classification of lung cancer stages

PATHOLOGICAL STAGES	PRIMARY TUMOR	REGIONAL LYMPH NODES	DISTANT METASTASIS
Occult cancer	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N0	
Stage IIIA	T1*	N2	M0
	T2	N2	
	T3	N1, N2	
Stage IIIB	T1 to 4	N3	M0
	T4†	N0 to 3	
Stage IV	T1 to 4	N0 to 3	M1

Source: Health Canada, Population and Public Health Branch (PPHB). Lung Cancer, Guidelines for Processing Specimens and Reporting Tumor Stage. Appendix 4 – TNM Classification. Available: http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/lung-poumon/lcg_i_e.html (consulted on April 1, 2004).

Legend

T = Primary tumor

TX = Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy

T0 = No evidence of primary tumor

Tis = Carcinoma *in situ*

T1 = Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus)*

T2 = Tumor with any of the following features of size or extent: more than 3 cm in greatest dimension; involves main bronchus, 2 cm or more distal to the carina; invades visceral pleura; associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T3 = Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium, or tumor in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or associated atelactasis or obstructive pneumonitis of the entire lung

T4 = Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, oesophagus, vertebral body or carina; separate tumor nodule(s) in the same lobe; tumor with malignant pleural effusion†

* The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1.

† Most pleural effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathological examinations of pleural fluid are negative for tumor, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgement dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as T1, T2, or T3. This also applies to pericardial effusions.

N = Regional lymph nodes

NX = Regional lymph nodes cannot be assessed
N0 = No regional lymph-node metastasis
N1 = Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, including involvement by direct extension
N2 = Metastasis in ipsilateral mediastinal and/or subcarinal lymph nodes
N3 = Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes

M = Distant Metastasis

MX = Distant metastasis cannot be assessed
M0 = No distant metastasis
M1 = Distant metastasis, includes separate tumor nodule(s) in a different lobe (ipsilateral or contralateral)

TABLE F-3

TNM classification of bladder cancer stages

PATHOLOGICAL STAGES	PRIMARY TUMOR	REGIONAL LYMPH NODES	DISTANT METASTASIS
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3a	N0	M0
Stage III	T3b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Multiple T	N1, N2 and N3	M0
	Multiple T	Multiple N	M1

Source: International Union Against Cancer (2002)

Legend

T = Primary tumor

TX = Primary tumor cannot be assessed
T0 = No evidence of primary tumor
Ta = Noninvasive papillary carcinoma
Tis = Carcinoma *in situ* (CIS), noninvasive flat carcinoma
T1 = Tumor has spread to subepithelial connective tissue
T2 = Tumor has spread to muscle
T3 = Tumor has spread to perivesical tissue (fatty tissue that surrounds the bladder) (T3a = tumor has spread microscopically and T3b = tumor has spread macroscopically)
T4 = Tumor has spread to any of the following: prostate, uterus, vagina, pelvic wall, or abdominal wall (T4a: Tumor has spread to the prostate, uterus, and/or vagina, and T4b: tumor has spread to the pelvic wall or the abdominal wall)

N = Regional lymph nodes

NX = Regional lymph nodes cannot be assessed
N0 = No regional lymph node metastasis
N1 = Metastasis in a single lymph node < 2 cm (4/5 inch)
N2 = Metastasis in a single lymph node > 2 cm but < 5 cm, or multiple lymph nodes < 5 cm
N3 = Metastasis in a lymph node > 5 cm

M = Distant Metastasis

MX = Distant metastasis cannot be assessed
M0 = No distant metastasis
M1 = One or more distant metastasis

APPENDIX G

COST COMPARISON OF PHOTOFRIN-MEDIATED PDT FOR LUNG CANCER (ACCORDING TO AXCAN PHARMA)

TREATMENT	LENGTH OF HOSPITAL STAY	COSTS	COMMENTS
Surgery	15.6 days	FF 40,700 Can$8,383	• Length of hospital stays and costs to be verified for Québec. • There is no information on individual cost items. • It is improbable that PDT can be administered only once without multiple interventions.
Chemotherapy (cisplatin + gemcitabin)	3 days (one day a week for 3 weeks)	FF 54,000 Can$11,122	
Radiotherapy	30 days (5 days a week for 6 weeks)	FF 8,960 to 17,000 Can$1,922 to $3,648	
PDT	2 days	FF 19,500 Can$4,016	

Source: Axcan Pharma, 2000b

REFERENCES

Ackroyd R, Brown NJ, Davis MF, Stephenson TJ, Marcus SL, Stoddard CJ, et al. Photodynamic therapy for dysplastic Barrett's oesophagus: A prospective, double blind, randomised, placebo controlled trial. Gut 2000;47(5):612–7.

Agence française de sécurité sanitaire des produits de santé (AFSSAPS). Répertoire des spécialités pharmaceutiques, 1997. Available: http://agmed.sante.gouv.fr/htm/7/pl5000c.htm (access fee; consulted on September 30, 2002).

Agence nationale d'accréditation et d'évaluation en santé (ANAES). Indications thérapeutiques des lasers en dermatologie, 1997. Available: http//www.anaes.fr (consulted on August 30, 2002).

Alderson D, Blazeby JM. Expanding metal stents in the gastrointestinal tract. Br J Surg 1995;82(11):1441–3.

American Lung Association. Facts about lung cancer, 2001. Available: http//www.lunusa.org/diseases/lungcanc.html (consulted on July 31, 2002).

American Society of Clinical Oncology. Clinical practice guidelines for the treatment of unresectable non-small-cell lung cancer. Adopted on May 16, 1997, by the American Society of Clinical Oncology. J Clin Oncol 1997;15(8):2996–3018.

Association des urologues du Québec. Guide de pratique, 2001. Available: http://www.auq.org/guidef.html (consulted on August 2, 2002).

Association pulmonaire canadienne. Cancer du poumon, 2002. Available: http://www.lung.ca/fr/maladies/cancers_poumon.html (consulted on August 3, 2002).

Axcan Pharma, Inc. Axcan receives Canadian approval for Photofrin in the treatment of high-grade dysplasia associated with Barrett's esophagus, 2003. Available: http://www.newswire.ca/en/releases/archive/March2003/20/c2455.html (consulted on November 5, 2003).

Axcan Pharma Inc. Recherche et développement. Thérapie photodynamique – Photofrin TPD. Available: http://www.axcan.com/axcan/francais/research/photodynamic.shtml (consulted on January 15, 2003).

Axcan Pharma Inc. Monographie du produit: Porfimer sodique stérile pour injection – photosensibilisant antinéoplasique. Vancouver: Axcan Pharma, 2000a.

Axcan Pharma inc. Photofrin TPD – proposition au MSSS du Québec. August 2000b.

Berkow R, ed. Gastroentérologie. In: Manuel Merck de diagnostic et thérapeutique. Paris: Éditions d'Après; 1994: 693–810.

Berkow R, ed. Pneumologie. In: Manuel Merck de diagnostic et thérapeutique. Paris: Éditions d'Après; 1994: 559–692.

Berkow R, ed. Urologie-Néphrologie. In: Manuel Merck de diagnostic et thérapeutique. 2nd ed., Paris: Éditions d'Après; 1994: 1553–664.

Boyer J, Robaszkiewicz M. Guidelines of the French Society of Digestive Endoscopy: Monitoring of Barrett's Esophagus. The Council of the French Society of Digestive Endoscopy. Endoscopy 2000;32(6):498–9.

Calzavara F, Tomio L, Corti L, Zorat PL, Barone I, Perrachia A, Norberto L, et al. Oesophageal cancer treated by photodynamic therapy alone or followed by radiation therapy. J Photochem Photobiol B 1990;6:167–74.

Canadian Association of Gastroenterology, Cockeram AW. Practice guidelines for evaluation of dysphagia. Mississauga, Ont.: CAG; 1998.

Canadian Medical Association / Association médicale canadienne. Guidelines for Canadian clinical practice guidelines / Principes directeurs concernant les guides de pratique clinique au Canada. [S.l.]: AMC, 1994. Quality of care program / Programme de la qualité des soins.

Canadian Task Force on the Periodic Health Examination, Health Canada. Canadian Guide to Clinical Preventive Health. Ottawa, Minister of Supplies and Services Canada; 1994.

Canto MI, Smith C, McClelland L, Kantsevoy S, Heath E, Zahurak M, Powe N. Randomized trial of PDT vs. stent for palliation of malignant dysphagia: Cost-effectiveness and quality of life. Gastrointest Endosc 2002;55(5): AB100 [abstract 600].

Ceburkov O, Gollnick H. Photodynamic therapy in dermatology. Eur J Dermatol 2000;10(7):568–76.

Center for Occupational Research and Development (CORD), Waco, Texas. Introduction to Lasers. Laser Electro-Optics Technology Curriculum (LEOT), 2001. Available: http://www.dewtronics.com/tutorials/lasers/leot/course01_mod01–01.html.

Chang SC, Bown SG. Photodynamic therapy: Applications in bladder cancer and other malignancies [review]. J Formos Med Assoc 1997;96:853–63.

Chen Q, Hetzel FW. Laser dosimetry studies in the prostate. J Clin Laser Med Surg 1998;16:9–12.

Cortese DA, Edell ES, Kinsey JH. Photodynamic therapy for early stage squamous cell carcinoma of the lung. Mayo Clin Proc 1997;72(7):595–602.

Corti L, Skarlatos J, Boso C, Cardin F, Kosma L, Koukourakis MI, et al. Outcome of patients receiving photodynamic therapy for early esophageal cancer. Int J Radiat Oncol Biol Phys 2000;47(2):419–24.

Courtay A, Cazes A, Baffert S, Perrin JP, Fery-Lemonnier E. Comité d'évaluation et de diffusion des innovations technologiques. Dossier CEDIT: Photothérapie dynamique en gastro-entérologie et en ORL. Paris: Assistance publique – Hôpitaux de Paris; 1999.

D'Hallewin MA, Baert L. Long-term results of whole bladder wall photodynamic therapy for carcinoma in situ of the bladder. Urology 1995;45(5):763–7.

Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 1998;83(10):2049–53.

Diamond I, Granelli SG, McDonagh AF, Nielsen S, Wilson CB, Jaenicke R. Photodynamic therapy of malignant tumours. Lancet 1972;2(7788):1175–7.

Diaz-Jimenez JP, Martinez-Ballarin JE, Llunell A, Farrero E, Rodriguez A, Castro MJ. Efficacy and safety of photodynamic therapy versus Nd-YAG laser resection in NSCLC with airway obstruction. Eur Respir J 1999;14(4):800–5.

Diomed Inc. 630 PDT Laser for Photofrin, porfimer sodium. London: Diomed; 2000.

Dougherty TJ. An update on photodynamic therapy applications. J Clin Laser Med Surg 2002; 20(1):3–7.

Dougherty TJ, Gomer CJ, Henderson BW, et al. Photodynamic therapy. J Natl Cancer Inst 1998; 90(12):889–905.

Enzinger PC, Mayer RJ. Esophageal cancer. New Engl J Med 2003;349(23):2241–52.

Étienne J, Dorme N, Bourg-Heckly G, Raimbert P, Fekete F. Local curative treatment of superficial adenocarcinoma in Barrett's esophagus. First results of photodynamic therapy with a new photosensitizer. Bull Acad Natl Med 2000;184(8):1731–44.

European Society of Medical Oncology (ESMO), 2002. Minimum clinical recommendations, levels of evidence and grades of recommendations (as used by ASCO Guidelines). Available: http://www.esmo.org/reference/referenceGuidelines/html/levels_of_evidence_htm.

Faivre J, Forman D, Esteve J, Gatta G. Survival of patients with oesophageal and gastric cancers in Europe. Eur J Cancer 1998;34(14):2167–75.

Fleshner NE, Herr HW, Stewart AK, Murphy GP, Mettlin C, Menck HR. The National Cancer Data Base report on bladder carcinoma. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer 1996;78(7):1505–13.

Food and Drug Administration (FDA), United States. Photofrin homologation, 2000. Available: http://www.fda.gov/cder/da/da1298.htm (consulted on July 27, 2002).

Foote CS. Definition of type I and type II photosensitised oxidation. Photochem Photbiol 1991;54(5):659.

Freitas D, Gouveia H, Sofia C, Cabral JP, Donato A. Endoscopic Nd-YAG laser therapy as palliative treatment for esophageal and cardial cancer. Hepatogastroenterology 1995;42(5):633–7.

Greenwald BD. Photodynamic therapy for esophageal cancer. Update [review]. Chest Surg Clin North Am 2000;10(3);625–37.

Grosjean P, Wagnieres G, Fontolliet C, van den Bergh H, Monnier P. Clinical photodynamic therapy for superficial cancer in the oesophagus and the bronchi: 514 nm compared with 630 nm light irradiation after sensitization with Photofrin II. Br J Cancer 1998;77(11):1989–95.

Hamilton SR. Pathogenesis of columnar cell lined (Barrett's) esophagus. In: Spechler SJ, Goyal RK, eds. Barrett's esophagus: pathophysiology, diagnosis, and management. New York: Elsevier; 1985: 2937.

Health Canada, Population and Public Health Branch (PPHB). Lung Cancer, Guidelines for Processing Specimens and Reporting Tumour Stage. Appendix 4: TNM Classification. Available: http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/lung-poumon/lcg_i_e.html (consulted on April 1, 2004).

Health Canada, Therapeutic Products Directorate. Drug Product Database (DPD). Available: http://www.hc-sc.gc.ca/hpb/drugs-dpd/ (consulted on January 15, 2003).

Herr HW. Editorial comment. In: Nseyo UO, Shumaker B, Klein EA, Sutherland K. Photodynamic therapy using porfimer sodium as an alternative to cystectomy in patients with refractory transitional cell carcinoma in situ of the bladder. J Urol 1998;160(1):44.

Heier SK, Rothman KA, Heier LM, Rosenthal WS. Photodynamic therapy for obstructing esophageal cancer: Light dosimetry and randomized comparison with Nd:YAG laser therapy. Gastroenterology 1995;109(1):63–72.

Institut national de la santé publique du Québec (INSPQ), Ministère de la Santé et des Services sociaux. Données sur la mortalité, 2001. Available: http://www.inspq.qc.ca/medias/communiques/ (consulted on July 19, 2001).

Institute for Clinical Systems Improvement (ICSI). Photodynamic therapy for head and neck, tracheobronchial, and esophageal cancer. Technology Assessment Report Update TA No. 39; October 2002: 8 pp.

Institute for Clinical Systems Improvement (ICSI). Photodynamic therapy for head and neck, tracheobronchial, and esophageal cancer. Technology Assessment Report TA No. 39; September 1997: 28 pp.

International Union Against Cancer. TNM Classification of Malignant Tumours. Sobin LH, Wittekind C, ed. 6th ed. New York: J Wiley; 2002.

Jin ML, Yang BQ, Zhang W, Ren P. Combined treatment with photodynamic therapy and chemotherapy for advanced cardiac cancers. J Photochem Photobiol B 1992;12(1):101–6.

Kato H. Photodynamic therapy for lung cancer: A review of 19 years' experience [review]. J Photochem Photobiol B février 1998;42(2):96–9.

Kessel D, Luo Y. Mitochondrial photodamage and PDT-induced apoptosis. J Photochem Photobiol B 1998;42:89–95.

Kriegmair M, Baumgartner R, Lumper R, Waidelich R, Hofstetter A. Early clinical experience with 5-aminolevulinic acid for the photodynamic therapy of superficial bladder cancer. Br J Urol 1996;77:667–71.

Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999;340(11):825–31.

Lightdale CJ. Role of photodynamic therapy in the management of advanced esophageal cancer [review]. Gastrointest Endosc Clin N Am 2000;10(3):397–408.

Lightdale CJ. Esophageal cancer. American College of Gastroenterology. Am J Gastroenterol 1999; 94(1):20–9.

Lightdale CJ, Heier SK, Marcon NE, McCaughan JS Jr, Gerdes H, Overholt BF, et al. Photodynamic therapy with porfimer sodium versus thermal ablation therapy with Nd:YAG laser for palliation of esophageal cancer: A multicenter randomized trial. Gastrointest Endosc 1995;42(6):507–12.

Lipson RL, Baldes EJ. The photodynamic properties of a particular hematoporphyrin derivative. Arch Dermatol 1960;82 (October):508–16.

Litle VR, Luketich JD, Christie NA, Buenaventura PO, Alvelo-Rivera M, McCaughan JS, et al. Photodynamic therapy as palliation for esophageal cancer: experience in 215 patients. Ann Thorac Surg 2003;76(5):1687–92.

Litle L, Molpus K, Hasan T, Wilson BC. Light dosimetry for intra peritoneal photodynamic therapy in a murine xenograft model of human epithelial ovarian carcinoma. Photochem Photobiol 1998;68:281–8.

Luketich JD, Christie NA, Buenaventura PO, Weigel TL, Keenan RJ, Nguyen NT. Endoscopic photodynamic therapy for obstructing esophageal cancer: 77 cases over a 2-year period. Surg Endosc 2000;14(7):653–7.

Luketich JD, Nguyen NT, Weigel TL, Keenan RJ, Ferson PF, Belani CP. Photodynamic therapy for treatment of malignant dysphagia. Surg Laparosc Endosc Percutan Tech 1999;9(3):171–5.

Maier A, Tomaselli F, Matzi V, Rehak P, Pinter H, Smolle-Jüttner FM. Photosensitization with hematoporphyrin derivative compared to 5-aminolaevulinic acid for photodynamic therapy of esophageal carcinoma. Ann Thorac Surg 2001a;72:1136–40 (also published by Maier et al. In: Lasers Surg Med 2001b, see reference).

Maier A, Tomaselli F, Matzi V, Rehak P, Pinter H, Smolle-Jüttner FM. Does new photosensitizer improve photodynamic therapy in advanced esophageal carcinoma? Lasers Surg Med 2001b;29:323–7 (also published by Maier et al. In: Ann Thorac Surg 2001a, see reference).

Maier A, Tomaselli F, Gebhard F, Rehak P, Smolle J, Smolle-Jüttner FM. Palliation of advanced esophageal carcinoma by photodynamic therapy and irradiation. Ann Thorac Surg 2000;69:1006–9.

Maier A, Pinter H, Friehs GB, Renner H, Smolle-Juttner FM. Self-expandable coated stent after intraluminal treatment of esophageal cancer: a risky procedure? Ann Thorac Surg 1999;67(3):781–4.

Marcon NE. Photodynamic therapy and cancer of the esophagus. Semin Oncol 1994;21:20–3.

Marengo S, Houle D, Brasseur N, Nguyen TL, Ouellet R, van Lier J. Mesure du rendement d'oxygène singulet généré à partir de photosensibilisateurs tumoraux à base de naphtalocyanines. J Chim Phys 1994;91:1211–3.

McCaughan JS. Survival after photodynamic therapy to non-pulmonary metastatic endobronchial tumors. Lasers Surg Med 1999;24(3):194–201.

McCaughan JS. Photodynamic therapy of malignancies: A clinical manual. Austin: RG Landes; 1972.

Medicare Services Advisory Committee. Photodynamic therapy for skin and mucosal cancer. Canberra, Australia: Medicare Services Advisory Committee; 1999. Notes: Final Assessment Report.

Medicines Evaluation Board (MEB). Photofrin® homologation, 2001. Available: http://www.cbg-meb.nl/uk/prodinfo/index.htm (consulted on September 30, 2002).

Mimura S, Ito Y, Nagayo T, Ichii M, Kato H, Sakai H, et al. Cooperative clinical trial of photodynamic therapy with Photofrin II and excimer dye laser for early gastric cancer. Lasers Surg Med 1996;19(2):168–72.

Ministère de la Santé et des Services sociaux du Québec (MSSS). Fichiers des tumeurs du Québec; 2002.

Mlkvy P, Messmann H, Regula J, Conio M, Pauer M, Millson CF, et al. Photodynamic therapy for gastrointestinal tumors using three photosensitizers—ALA induced PPIX, Photofrin and MTHPC. A pilot study. Neoplasma 1998;45(3):157–61.

Mlkvy P, Messmann H, Debinski H, Regula J, Conio M, MacRobert A, et al. Photodynamic therapy for polyps in familial adenomatous polyposis—a pilot study. Eur J Cancer 1995;31A(7-8): 1160–5.

Moghissi K, Dixon K, Thorpe JA, Stringer M, Moore PJ. The role of photodynamic therapy (PDT) in inoperable oesophageal cancer. Eur J Cardiothorac Surg 2000;17(2):95–100.

Moghissi K, Dixon K, Stringer M, Freeman T, Thorpe A, Brown S. The place of bronchoscopic photodynamic therapy in advanced unresectable lung cancer: Experience of 100 cases. Eur J Cardiothorac Surg 1999;5(1):1–6.

Moghissi K. Surgical resection for Stage I cancer of the oesophagus and cardia. Br J Surg 1992; 79:935–7.

Morey SS. American Urological Association issues guidelines on the management of bladder cancer. Am Fam Physician 2000;61(12):3734, 3736.

Morton CA, Whitehurst C, Moseley H, McColl JH, Moore JV, Mackie RM. Comparison of photodynamic therapy with cryotherapy in the treatment of Bowen's disease. Br J Dermatol 1996;135(5):766–71.

Moskal TL, Dougherty TJ, Urschel JD, Antkowiak JG, Regal AM, Driscoll DL, Takita H. Operation and photodynamic therapy for pleural mesothelioma: 6-year follow-up. Ann Thorac Surg 1998; 66(4):1128–33.

Narayan S, Sivak MV Jr. Palliation of esophageal carcinoma. Laser and photodynamic therapy [review]. Chest Surg Clin North Am 1994;4(2):347–67.

National Cancer Institute of Canada (NCIC), Canadian Cancer Society. Canadian Cancer Statistics 2002. Toronto: National Cancer Institute of Canada; 2002.

National Cancer Institute. Surveillance epidemiology and results: Esophagus cancer (invasive). Available: http://seer.cancer.gov/csr/1973_1999/esoph.pdf (consulted on July 9, 2002).

National Cancer Institute. Surveillance epidemiology and results: Lung and bronchus cancer (invasive). Available: http://seer.cancer.gov/csr/1973_1999/lung.pdf (consulted on July 9, 2002).

National Cancer Institute. Surveillance epidemiology and results: Urinary bladder cancer (invasive and in situ). Available: http://seer.cancer.gov/csr/1973_1999/bladder.pdf (consulted on July 9, 2002).

Nishioka NS. Photodynamic therapy and the GI tract. Gastrointestinal Unit, Massachusetts General Hospital, Boston MA, 1999 [unpublished review].

Ninane V. La photothérapie dans le traitement des cancers bronchiques. Rev Mal Respir November 1999;16(4 Pt 2):633–9.

Nishioka NS. Drug, light and oxygen: A dynamic combination in the clinic. Gastroenterology 1998; 114:604–6.

Nseyo UO, DeHaven J, Dougherty TJ, Potter WR, Merrill DL, Lundahl SL, Lamm DL. Photodynamic therapy (PDT) in the treatment of patients with resistant superficial bladder cancer: A long-term experience. J Clin Laser Med Surg 1998a;16(1):61–8.

Nseyo UO, Shumaker B, Klein EA, Sutherland K. Photodynamic therapy using porfimer sodium as an alternative to cystectomy in patients with refractory transitional cell carcinoma in situ of the bladder. Bladder Photofrin study group. J Urol 1998b;160(1):39–44.

Overholt BF, Panjehpour M. Photodynamic therapy in the management of Barrett's esophagus with dysplasia. J Gastrointest Surg 2000;4(2):129–30.

Overholt BF, Panjehpour M, Haydek JM. Photodynamic therapy for Barrett's esophagus: Follow-up in 100 patients. Gastrointest Endosc 1999;49:1–7.

Overholt BF. Results of photodynamic therapy in Barrett's esophagus: A review. Can J Gastroenterol juin1999;13(5):393–6.

Overholt BF, Panjehpour M. Photodynamic therapy for Barrett's esophagus: Clinical update. Am J Gastroenterol 1996a;91:1719–23.

Overholt BF, Panjehpour M. Photodynamic therapy in Barrett's esophagus. J Clin Laser Med Surg octobre 1996b;14(5):245–9.

Overholt BF, Panjehpour M. Barrett's esophagus: Photodynamic therapy for ablation of dysplasia, reduction of specialized mucosa, and treatment of superficial esophageal cancer. Gastrointest Endosc 1995a;42:64–70.

Overholt BF, Panjehpour M. Photodynamic therapy in Barrett's esophagus: Reduction of specialized mucosa, ablation of dysplasia and treatment of superficial esophageal cancer. Sem Surg Oncol 1995b;11:372–6.

Panjehpour M, Overholt BF, Haydek JM, Lee SG. Results of photodynamic therapy for ablation of dysplasia and early cancer in Barrett's esophagus and effect of oral steroids on stricture formation. Am J Gastroenterol 2000;95(9):2177–84.

Pass HI, Temeck BK, Kranda K, Thomas G, Russo A, Smith P, et al. Phase III randomized trial of surgery with or without intraoperative photodynamic therapy and postoperative immunochemotherapy for malignant pleural mesothelioma. Ann Surg Oncol 1997;4(8):628–33.

Patterson MS, Wilson BC. Photodynamic therapy. In: Dyh JV, ed. The modern technology of radiation oncology. Madison Medical Physics Publishing; 1999: 941–80.

Peterson WG, Mayrand S. Oesophage. In: Thomson ABR, Shaffer EA, eds. Principes fondamentaux de gastro-entérologie. Edmonton: Association canadienne de gastro-entérologie; 2000:101–45.

Ponec RJ, Kimmey MB. Endoscopic therapy of esophageal cancer (Review). Surg Clin North Am 1997;77(5):1197–217.

PSL Group (2002). Photofrin photodynamic therapy for treating Barrett's esophagus. Available: http://www.pslgroup.com/dg/1dfc-4a.htm.

Rivellese MJ, Baumal CR. Photodynamic therapy of eye diseases. J Ophthalmic Nurs Technol 2000;19(3):134–41.

Sampliner RE, and the Practice Parameters Committee of the American College of Gastroentereology. Updated guidelines for the diagnosis, surveillance, and therapy of Barrett's esophagus—Practice guidelines. Am J Gastroenterol 2002;97(8):1888–95.

Sampliner RE and the Practice Parameters Committee of the American College of Gastroentereology. Practice guidelines on the diagnosis, surveillance, and therapy of Barrett's esophagus. Am J Gastroenterol 1998;93:1028–32.

Savary JF, Grosjean P, Monnier P, Fontolliet C, Wagnieres G, Braichotte D, van den Bergh H. Photodynamic therapy of early squamous cell carcinomas of the esophagus: A review of 31 cases. Endoscopy 1998;30(3):258–65.

Scheider DM, Siemens M, Cirocco M, Haber GB, Kandel G, Kortan P, Marcon NE. Photodynamic therapy for the treatment of tumor ingrowth in expandable esophageal stents. Endoscopy 1997;29(4):271–4.

Schnell TG, Sontag SJ, Chejfec G, Aranha G, Metz A, O'Connell S, et al. Long-term nonsurgical management of Barrett's esophagus with high-grade dysplasia. Gastroenterology 2001;120:1607–19.

Shaheen N, Ransohoff DF. Gastroesophageal reflux, Barrett esophagus, and esophageal cancer—Scientific review. J Am Med Assoc 2002;287(15):1972–81.

Shaheen NJ, Crosby MA, Bozymski EM, Sandler RS. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? Gastroenterology 2000;119:333–8.

Sharman WM, Allen CM, van Lier JE. Photodynamic therapeutics: Basic principles and clinical applications. Drug Discov Today 1999;4(11):507–17.

Sharpe DAC, Moghissi K. Resectional surgery in carcinoma of the oesophagus and cardia; what influences long-term survival? Eur J Cardiothorac Surg 1996;10:359–64.

Shikowitz MJ, Abramson AL, Freeman K, Steinberg BM, Nouri M. Efficacy of DHE photodynamic therapy for respiratory papillomatosis: Immediate and long-term results. Laryngoscope 1998; 108(7):962–7.

Sibata CH, Colussi VC, Olenick NL, Kinsella TJ. Photodynamic therapy in oncology [Review]. Expert Opin Pharmacother 2001;2(6):917–27.

Sibille A, Lambert R, Souquet JC, Sabben G, Descos F. Long-term survival after photodynamic therapy for esophageal cancer. Gastroenterology 1995;108(2):337–44.

Smith R, Hahn S. Photodynamic therapy. Curr Probl Cancer 2002;26:61–108.

Spechler SJ. Barrett's Esophagus. Clinical practice. N Engl J Med 2002a;346(11):836–42.

Spechler SJ. Management of Barrett's esophagus. Up to date 2002b:1–14. Available: http://www.uptodate.com/patient_info/topicpages/topics/EsophDis/10231.asp (consulted on 17 January 2003).

Stables GI, Ash DV. Photodynamic therapy. Cancer Treat Rev 1995;21(4):311–23.

Star WM. Light dosimetry in vivo. Phys Med Biol 1997;42:763–87.

Statistics Canada. Life tables, Canada, provinces and territories. Available: http://www.statcan.ca/Daily/English/020823/d020823f.htm (consulted on July 25, 2002).

Sturgess RP, Morris AI. Metal stents in the oesophagus. Gut 1995;37(5):593–4.

Swisher SG, Deford L, Merriman KW, Walsh GL, Smythe R, Vaporicyan A, et al. Effects of operative volume on morbidity, mortality, and hospital use after esophagectomy for cancer. J Thorac Cardiovasc Surg 2000;119:1126–32.

Teppo E. Nd:YAG Laser: Versatile material works in diverse applications. Photonics Design & Solutions, Photonics Spectra; 1998:135–8.

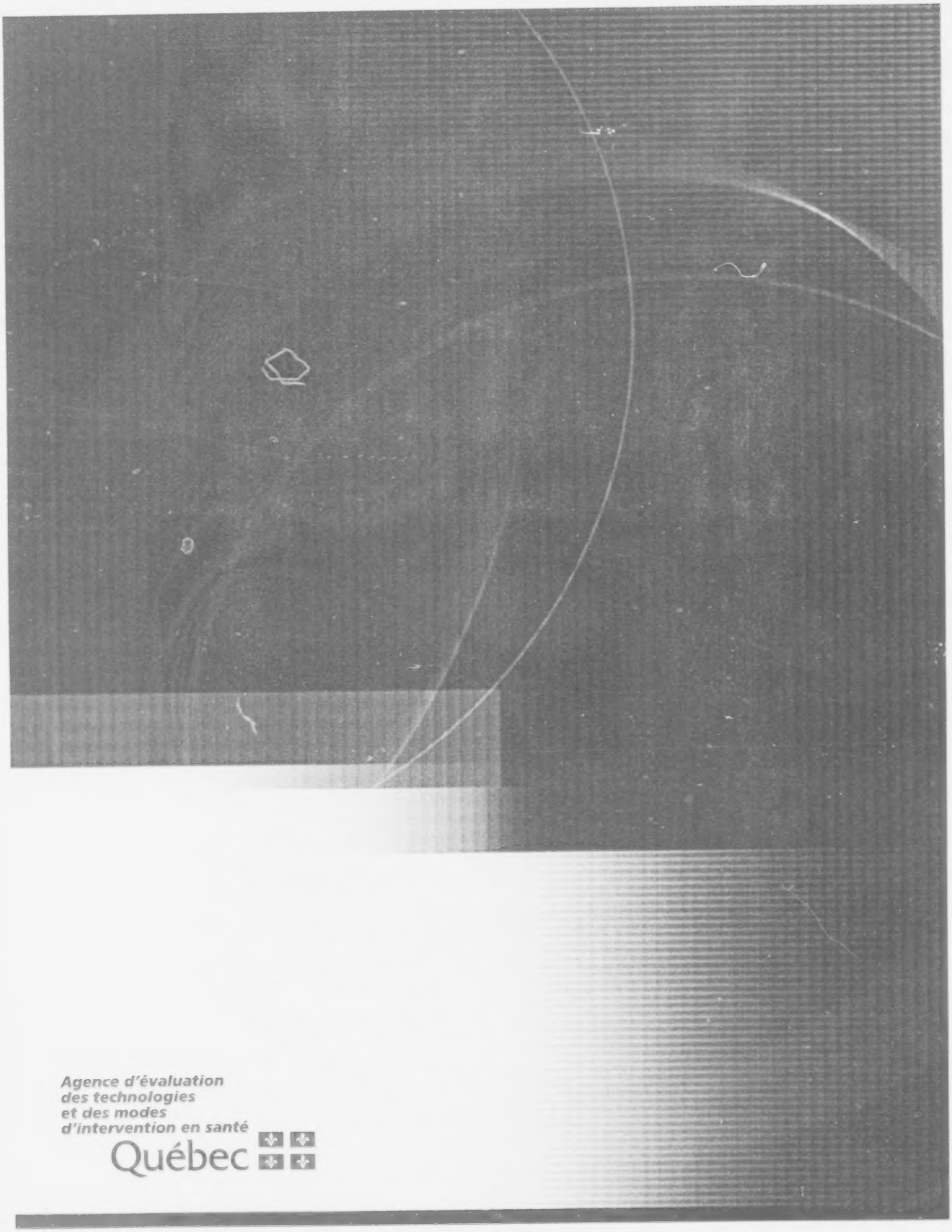
Van den Boogert J, van Hillegersberg R, Siersema PD, de Bruin RWF, Tilanus HW. Endoscopic ablation therapy for Barrett's esophagus with high-grade dysplasia: A review. Am J Gastroenterol 1999;94:1153–60.

Vulcan TG, Zhu TC, Rodriguez CE, Hsi A, Fraker DL, Baas P, et al. Comparison between isotropic and nonisotropic dosimetry systems during intraperitoneal photodynamic therapy. Lasers Surg Med 2000;26(3):292–301.

Walther MM, Delaney TF, Smith PD, Friauf WF, Thomas GF, Shawker TH, et al. Phase I trial of photodynamic therapy in the treatment of recurrent superficial transitional cell carcinoma of the bladder. Urology 1997;50(2):199–206.

Wang KK, Sampliner RE. Mucosal ablation therapy of Barrett esophagus. Mayo Clinic Proc 2001; 76(4):433–7.

World Cancer Research International. Research and Cancer in International Sciences (Newsletters, 1997). Available: http://206.239.24.80/research/researchandcancer.lasso? (consulted on March 23, 2002).



Agence d'évaluation
des technologies
et des modes
d'intervention en santé

Québec